DERWENT-ACC-NO: 2003-092803

DERWENT-WEEK: 200315

TITLE: Inhibition of tumor cell proliferation in colon cancer, by oral administration of gastric retention solid irinotecan dosage/liquid for stomach-release, such that irinotecan is converted to active lactone metabolite

INVENTOR: FLESHNER-BARAK, M; LERNER, E I ; ROSENBERGER, V

PATENT-ASSIGNEE: TEVA PHARM IND LTD[TEVAN] , TEVA PHARM USA INC[TEVAN]

PRIORITY-DATA: 2001US-273428P (March 5, 2001)

WO0208100123 2001

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200270021 A1	September 12, 2002	E	062	A61K 051/00

DESIGNATED-STATES: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
WO 200270021A1	N/A	2001WO-US49305	December 20, 2001

INT-CL (IPC): A61K051/00

RELATED-ACC-NO: 2002-205919, 2002-241287 , 2003-155983

ABSTRACTED-PUB-NO: WO 200270021A

BASIC-ABSTRACT:

NOVELTY - Orally administered gastric retention dosage/liquid (GRD) of irinotecan is released in stomach and converted into metabolite (M) before bloodstream-absorption. (M) exists in active lactone- (AL) and inactive hydroxy acid-forms. Bioavailability (BA) of AL is more than BA of LF when (I) is administered in non-GRD. This results in enhanced systemic delivery of AL to tumor for cell proliferation inhibition.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a solid dosage form, comprising an antineoplastic agent (ANA) (absorbable through stomach, jejunum or duodenum-lining) and a gastric retention vehicle composition (GRVC) comprising a hydrogel. The dosage expands upon contact with gastric fluid. After ingestion GRVC expands to retain the dosage in stomach for a prolonged period; and

(2) a liquid composition comprising a gelling agent. After ingestion of GRVC gels/precipitates to retain the dosage in stomach for 3 hours or more.

ACTIVITY - Cytostatic.

No biological data given.

MECHANISM OF ACTION - None given.

USE - For inhibiting tumor cell proliferation accompanied by metastatic

carcinoma of colon, rectum, testicular tumors, (non-)small cell lung-, ovarian-
or breast-cancer.

ADVANTAGE - The gastric treatment dosage forms are adapted for sustained,
delayed and/or pulsed release. The method improves gastric oral delivery of
irinotecan compared to intravenous delivery, and improves sustained low dose
administration of irinotecan over less frequent, high dose treatment. The
ability to administer irinotecan orally in a home setting permits increased
dosage frequency without inconvenience to the patient or care giver.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: INHIBIT TUMOUR CELL PROLIFERATION COLON CANCER ORAL ADMINISTER
GASTRIC RETAIN SOLID DOSE LIQUID STOMACH RELEASE CONVERT ACTIVE
LACTONE METABOLITE

DERWENT-CLASS: A96 B02 B05

CPI-CODES: A12-V01; B02-D; B04-C02A2; B04-C02B; B04-C02D; B04-C02F; B04-C03A;
B04-N02; B06-A02; B06-A03; B06-D18; B06-E05; B12-M03; B12-M07;
B14-H01;

CHEMICAL-CODES:
Chemical Indexing M2 *01*
Fragmentation Code
D011 D013 D016 D019 D022 E570 F011 F014 F019 F433
F499 H1 H121 H2 H201 H211 H4 H401 H421 H8
J5 J522 K0 L4 L463 L9 L941 L942 M210 M212
M240 M282 M320 M412 M431 M511 M522 M530 M540 M782
M904 M905 P633 R022 R023 R024 R038
Ring Index
41300
Specfic Compounds
A035HK A035HT A035HM

Chemical Indexing M6 *02*
Fragmentation Code

M905 R022 R023 R024 R280

Chemical Indexing M2 *03*
Fragmentation Code
D011 D014 D019 D160 D240 H4 H403 H422 H441 H5
H521 H541 H8 J5 J521 K0 L8 L814 L821 L835
L9 L942 M113 M126 M141 M210 M211 M240 M272 M281
M282 M320 M412 M431 M512 M520 M531 M540 M782 M904
M905 P633 R022 R023 R024 R038
Ring Index
01652 01652 04205 04205
Specfic Compounds
08748K 08748T 08748M 10115K 10115T 10115M

Chemical Indexing M2 *04*
Fragmentation Code
D021 D024 D025 D026 D030 D220 G010 G019 G100 H4
H403 H462 H481 H8 J0 J014 J2 J221 J231 J262
J3 J331 J5 J561 M1 M123 M136 M210 M211 M240
M262 M282 M283 M312 M321 M332 M344 M349 M371 M391
M412 M431 M511 M520 M533 M540 M782 M904 M905 P633
R022 R023 R024 R038
Ring Index
68515
Specfic Compounds
18653K 18653T 18653M

Chemical Indexing M2 *05*
Fragmentation Code
F012 F013 F014 F016 F123 G020 G022 G029 G034 G038
G420 H1 H100 H121 H4 H405 H421 H442 H461 H481
H5 H521 H541 H8 J5 J581 K0 L8 L817 L821
L834 L9 L951 M1 M126 M141 M210 M211 M240 M272
M281 M311 M321 M342 M349 M381 M391 M413 M431 M510
M521 M531 M540 M782 M904 M905 M910 P633 R022 R023
R024 R038
Specfic Compounds
02028K 02028T 02028M 08024K 08024T 08024M
Registry Numbers
2028U

Chemical Indexing M2 *06*
Fragmentation Code
D011 D012 D016 D019 D023 D026 D029 D030 E330 E350
H2 H211 H4 H402 H421 H461 H5 H541 H8 J0
J014 J2 J211 J251 J261 J3 J371 M1 M115 M210
M211 M212 M240 M262 M272 M281 M282 M283 M320 M412
M431 M512 M520 M530 M540 M782 M904 M905 M910 P633

R022 R023 R024 R038
Ring Index
11065 11065 13275 13275
Specfic Compounds
00125K 00125T 00125M 17770K 17770T 17770M
Registry Numbers
0125U

Chemical Indexing M2 *07*
Fragmentation Code
F012 F013 F014 F015 F016 F123 G017 G019 G100 H4
H405 H444 H8 J0 J014 J2 J222 J232 K0 L8
L814 L821 L831 M1 M121 M123 M129 M136 M139 M280
M311 M321 M342 M373 M391 M413 M431 M510 M521 M533
M540 M782 M904 M905 P633 R022 R023 R024 R038
Specfic Compounds
06321K 06321T 06321M 11956K 11956T 11956M

Chemical Indexing M1 *08*
Fragmentation Code
A111 A960 C710 M423 M431 M630 M782 M904 M905 P633
R022 R023 R024 R038
Specfic Compounds
A002YK A002YT A002YM

Chemical Indexing M1 *09*
Fragmentation Code
F011 F012 F423 H2 H211 H7 H713 H721 J5 J521
L9 L941 M210 M212 M273 M281 M320 M423 M431 M510
M521 M530 M540 M782 M904 M905 P633 R022 R023 R024
R038
Specfic Compounds
A002WK A002WT A002WM

Chemical Indexing M1 *10*
Fragmentation Code
M423 M431 M782 M905 P633 R022 R023 R024 R038
Specfic Compounds
A00CUK A00CUT A00CUM

Chemical Indexing M1 *11*
Fragmentation Code
J0 J011 J1 J111 J2 J211 K0 L8 L811 L815
L817 L818 L831 L832 M210 M211 M272 M280 M281 M320
M423 M431 M520 M523 M530 M540 M782 M904 M905 P633
R022 R023 R024 R038
Specfic Compounds
17032K 17032T 17032M

Chemical Indexing M1 *12*
Fragmentation Code
M423 M431 M782 M904 M905 P633 R022 R023 R024 R038
Specfic Compounds
24033K 24033T 24033M

Chemical Indexing M1 *13*
Fragmentation Code
A220 A960 C710 K0 K4 K421 L8 L815 L831 M423
M431 M630 M782 M904 M905 P633 R022 R023 R024 R038
Specfic Compounds
24036K 24036T 24036M

Chemical Indexing M1 *14*
Fragmentation Code
K0 L8 L814 L816 L831 L832 M423 M431 M782 M904
M905 P633 R022 R023 R024 R038
Specfic Compounds
16377K 16377T 16377M

Chemical Indexing M1 *15*
Fragmentation Code
A111 A960 C710 J0 J011 J1 J111 M423 M431 M782
M904 M905 M910 P633 R022 R023 R024 R038
Specfic Compounds
06725K 06725T 06725M
Registry Numbers
1866U

Chemical Indexing M1 *16*
Fragmentation Code
H5 H521 H8 M210 M211 M272 M281 M320 M423 M431
M782 M904 M905 M910 P633 R022 R023 R024 R038
Specfic Compounds
01860K 01860T 01860M A02KXK A02KXT A02KXM
Registry Numbers
1860U

Chemical Indexing M1 *17*
Fragmentation Code
H5 H521 H8 K0 L6 L660 M210 M213 M231 M272
M281 M311 M321 M342 M383 M391 M423 M431 M782 M904
M905 P633 R022 R023 R024 R038
Specfic Compounds
06563K 06563T 06563M 15976K 15976T 15976M

UNLINKED-DERWENT-REGISTRY-NUMBERS: 0125U; 1860U ; 1866U ;

2028U

ENHANCED-POLYMER-INDEXING:
Polymer Index [1.1]
018 ; R01863*R D01 D11 D10 D23 D22 D31 D42 D50 D76 D86 F24 F29 F26
F34 H0293 P0599 G3623 ; M9999 M2186 ; M9999 M2200 ; M9999 M2379*R
; M9999 M2415
Polymer Index [1.2]
018 ; ND01 ; Q9999 Q8037 Q7987 ; Q9999 Q6791 ; Q9999 Q7523 ; K9745*R
; N9999 N6439 ; N9999 N6600
Polymer Index [1.3]
018 ; B9999 B3510*R B3372
Polymer Index [1.4]
018 ; Na 1A ; H0157
Polymer Index [2.1]
018 ; R07352 R06717 G3678 G3634 G3623 D01 D03 D11 D10 D23 D22 D31
D42 D50 D61 D76 D92 F24 F34 F38 F35 Na 1A H0293 P0599
Polymer Index [2.2]
018 ; ND01 ; Q9999 Q8037 Q7987 ; Q9999 Q6791 ; Q9999 Q7523 ; K9745*R
; N9999 N6439 ; N9999 N6600
Polymer Index [2.3]
018 ; B9999 B3510*R B3372
Polymer Index [3.1]
018 ; G3714*R P0599 D01 F70 ; R24039 G3714 P0599 D01 F70 ; R24040
G3714 P0599 D01 F70
Polymer Index [3.2]
018 ; G3623*R P0599 D01 ; R01860 G3678 G3634 D01 D03 D11 D10 D23
D22 D31 D42 D50 D76 D89 F24 F34 H0293 P0599 G3623 ; R01865 G3678
G3634 G3623 P0599 D01 D03 D11 D23 D31 D42 D50 D76 D92 F24 F26 F34
H0293 ; R16377 D01 P0599 G3623 ; R24036 G3623 D01 D03 D05 D11 D10
D23 D22 D24 D31 D32 D42 D46 D50 D60 D76 D86 D92 F24 F27 F29 F26
F34 F60 H0293 P0599 ; R24033 G3714 P0599 D01 F70 ; R06725 R07226
G3623 P0599 D01 D23 D22 D31 D42 D50 D61 D76 D86 F24 F28 F26 F34
F36 F35 Na 1A H0293
Polymer Index [3.3]

018 ; R17032 G3623 P0599 D01 ; M9999 M2200 ; M9999 M2028

Polymer Index [3.4]

018 ; R03005 G3678 G3634 D01 D03 D11 D10 D23 D22 D31 D42 D50 D76
D93 F24 F29 F26 F34 H0293 P0599 G3623 ; R06563 G3678 G3634 G3623
P0599 D01 D03 D11 D10 D23 D22 D31 D42 D50 F24 F26 F34 H0293 ; S9999
S1365

Polymer Index [3.5]

018 ; ND01 ; Q9999 Q8037 Q7987 ; Q9999 Q6791 ; Q9999 Q7523 ; K9745*R
; N9999 N6439 ; N9999 N6600

SECONDARY-ACC-NO:

CPI Secondary Accession Numbers: C2003-023088

L1 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 209370-55-8 REGISTRY
CN **DNA (rabbit carboxyl esterase Irinotecan-activating cDNA plus flanks) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF036930
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

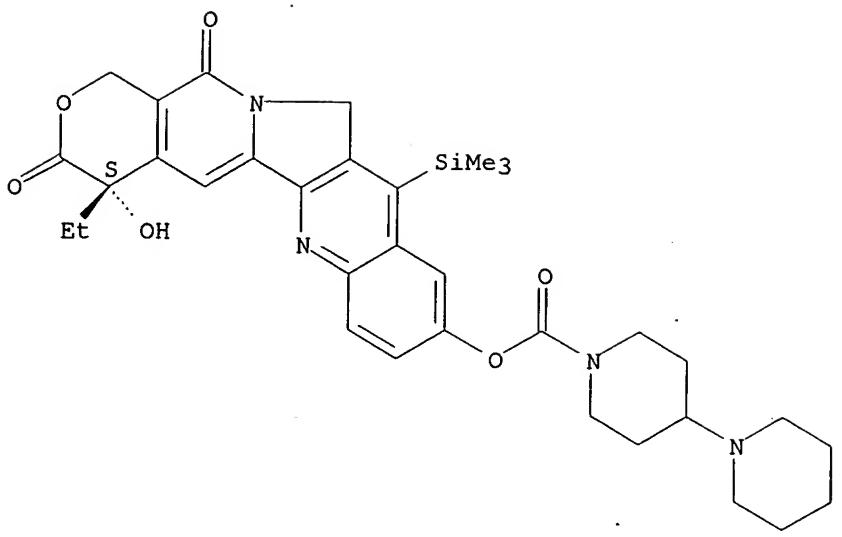
=> d l1 2-4 fide

L1 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 203173-72-2 REGISTRY
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4-ethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-11-(trimethylsilyl)-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4-ethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-11-(trimethylsilyl)-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, (S)-
OTHER NAMES:
CN **(20S)-7-(Trimethylsilyl)irinotecan**
FS STEREOSEARCH
MF C34 H42 N4 O6 Si
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL

Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C5N	NC5	6	C5N	46.156.1	2
C4N-C5N-C5N-C5O-C6	NC4-NC5-NC5-OC5-C6	5-6-6-6-6	C18N2O	7726.21.4	1

Absolute stereochemistry. Rotation (+).



Calculated Properties (CALC)

PROPERTY (CODE)	VALUE	CONDITION	NOTE
Bioconc. Factor (BCF)	1	pH 1	(1) ACD
Bioconc. Factor (BCF)	4.72	pH 4	(1) ACD
Bioconc. Factor (BCF)	35.2	pH 7	(1) ACD
Bioconc. Factor (BCF)	293	pH 8	(1) ACD
Bioconc. Factor (BCF)	4855	pH 10	(1) ACD
Boiling Point (BP)	850.7+/-65.0 deg C	760.0 Torr	(1) ACD
Enthalpy of Vap. (HVAP)	129.54+/-3.0 kJ/mol		(1) ACD
Flash Point (FP)	468.3+/-61.7 deg C		(1) ACD
H acceptors (HAC)	10		(1) ACD
H donors (HD)	1		(1) ACD
Koc (KOC)	1	pH 1	(1) ACD
Koc (KOC)	13.5	pH 4	(1) ACD
Koc (KOC)	101	pH 7	(1) ACD
Koc (KOC)	842	pH 8	(1) ACD
Koc (KOC)	13933	pH 10	(1) ACD
logD (LOGD)	0.57	pH 1	(1) ACD
logD (LOGD)	2.18	pH 4	(1) ACD
logD (LOGD)	3.05	pH 7	(1) ACD
logD (LOGD)	3.97	pH 8	(1) ACD
logD (LOGD)	5.19	pH 10	(1) ACD
logP (LOGP)	5.320+/-1.205		(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 1	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 4	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 7	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 8	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 10	(1) ACD
Molecular Weight (MW)	630.81		(1) ACD
pKa (PKA)	11.00+/-0.20	Most Acidic	(1) ACD
pKa (PKA)	9.33+/-0.20	Most Basic	(1) ACD
Vapor Pressure (VP)	8.75E-31 Torr	25.0 deg C	(1) ACD

(1) Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 ((C) 1994-2003 ACD)

5 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES IN FILE CAPLUS (1957 TO DATE)

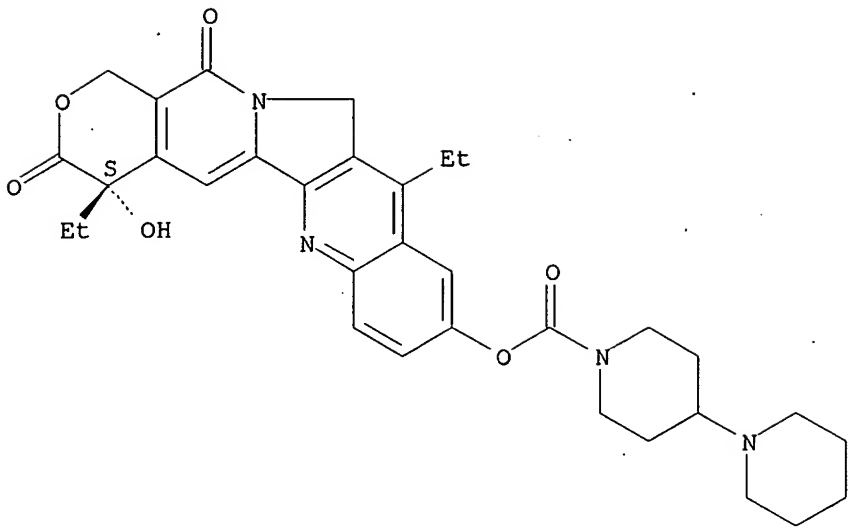
L1 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 100286-90-6 REGISTRY
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline, [1,4'-bipiperidine]-1'-carboxylic acid deriv.
CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride, (S)-
OTHER NAMES:
CN 7-Ethyl-10-[[4-(1-piperidyl)-1-piperidyl]carbonyloxy]camptothecin hydrochloride
CN Campto
CN Camptothecin 11
CN Camptothecin 11 hydrochloride
CN CPT 11
CN **Irinotecan hydrochloride**
CN Topotecin
CN U 101440E
FS STEREOSEARCH
DR 111348-33-5
MF C33 H38 N4 O6 . Cl H
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
CRN (97682-44-5)

Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C5N	NC5	6	C5N	46.156.1	2
C4N-C5N-C5N-C5O-C6	NC4-NC5-NC5-OC5-C6	5-6-6-6-6	C18N2O	7726.21.4	1

Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 2-A

● HCl

494 REFERENCES IN FILE CA (1957 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
495 REFERENCES IN FILE CAPLUS (1957 TO DATE)

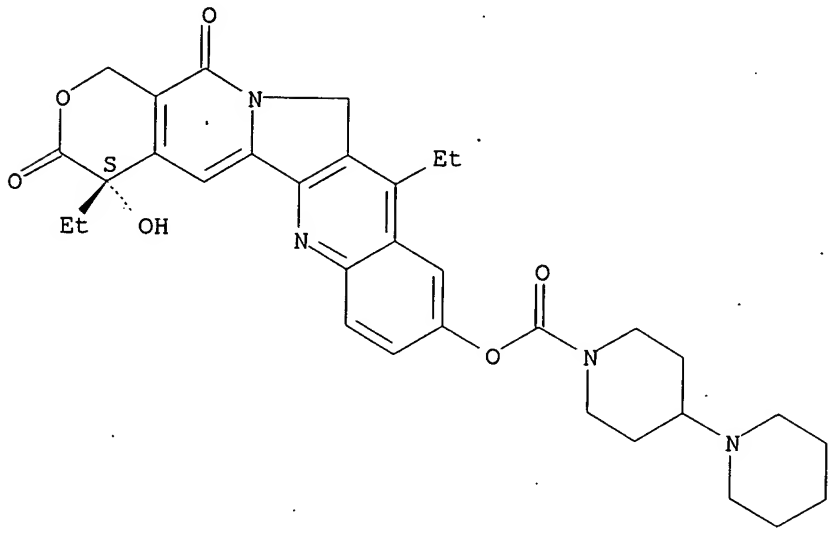
L1 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 97682-44-5 REGISTRY
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline, [1,4'-bipiperidine]-1'-carboxylic acid deriv.
CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, (S)-
OTHER NAMES:
CN **(+)-Irinotecan**
CN Camptosar
CN **Irinotecan**
FS STEREOSEARCH
MF C33 H38 N4 O6
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, IPA, MRCK*, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count

C5N	NC5	6	C5N	46.156.1	2
C4N-C5N-C5N-	NC4-NC5-NC5-	5-6-6-6-6	C18N2O	7726.21.4	1
C5O-C6	OC5-C6				

Absolute stereochemistry. Rotation (+).



Calculated Properties (CALC)

PROPERTY (CODE)	VALUE	CONDITION	NOTE
Bioconc. Factor (BCF)	1	pH 1	(1) ACD
Bioconc. Factor (BCF)	1	pH 4	(1) ACD
Bioconc. Factor (BCF)	2.51	pH 7	(1) ACD
Bioconc. Factor (BCF)	20.9	pH 8	(1) ACD
Bioconc. Factor (BCF)	346	pH 10	(1) ACD
Boiling Point (BP)	873.4+/-65.0 deg C	760.0 Torr	(1) ACD
Enthalpy of Vap. (HVAP)	132.98+/-3.0 kJ/mol		(1) ACD
Flash Point (FP)	482.0+/-61.7 deg C		(1) ACD
H acceptors (HAC)	10		(1) ACD
H donors (HD)	1		(1) ACD
Koc (KOC)	1	pH 1	(1) ACD
Koc (KOC)	1.61	pH 4	(1) ACD
Koc (KOC)	15.2	pH 7	(1) ACD
Koc (KOC)	127	pH 8	(1) ACD
Koc (KOC)	2102	pH 10	(1) ACD
logD (LOGD)	-1.11	pH 1	(1) ACD
logD (LOGD)	0.57	pH 4	(1) ACD
logD (LOGD)	1.54	pH 7	(1) ACD
logD (LOGD)	2.46	pH 8	(1) ACD
logD (LOGD)	3.68	pH 10	(1) ACD
logP (LOGP)	3.809+/-0.628		(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 1	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 4	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 7	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 8	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 10	(1) ACD

Molecular Weight (MW)	586.68		(1) ACD
pKa (PKA)	11.00+/-0.20	Most Acidic	(1) ACD
pKa (PKA)	9.33+/-0.20	Most Basic	(1) ACD
Vapor Pressure (VP)	1.31E-32 Torr	25.0 deg C	(1) ACD

(1) Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 ((C) 1994-2003 ACD)

659 REFERENCES IN FILE CA (1957 TO DATE)
17 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
662 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1600rkb

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Jun 13	Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and

```
                    right truncation
  NEWS 42   Jun 06  Simultaneous left and right truncation added to CBNB
  NEWS 43   Jun 06  PASCAL enhanced with additional data
  NEWS 44   Jun 20  2003 edition of the FSTA Thesaurus is now available
  NEWS 45   Jun 25  HSDB has been reloaded

  NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
                MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
                AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
  NEWS HOURS    STN Operating Hours Plus Help Desk Availability
  NEWS INTER    General Internet Information
  NEWS LOGIN    Welcome Banner and News Items
  NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
  NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
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FILE 'HOME' ENTERED AT 14:20:28 ON 01 JUL 2003

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:20:37 ON 01 JUL 2003
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provided by InfoChem.

STRUCTURE FILE UPDATES:   30 JUN 2003  HIGHEST RN 540462-79-1
DICTIONARY FILE UPDATES:  30 JUN 2003  HIGHEST RN 540462-79-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s irinotecan
L1             4 IRINOTECAN

=> file caplus uspatfull biosis scisearch europatfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
```

FULL ESTIMATED COST 4.62 4.83

FILE 'CAPLUS' ENTERED AT 14:21:13 ON 01 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'USPATFULL' ENTERED AT 14:21:13 ON 01 JUL 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 14:21:13 ON 01 JUL 2003
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FILE 'SCISEARCH' ENTERED AT 14:21:13 ON 01 JUL 2003
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FILE 'EUROPATFULL' ENTERED AT 14:21:13 ON 01 JUL 2003
COPYRIGHT (c) 2003 WILA Verlag Muenchen (WILA)

=> s l1
L2 4146 L1

=> s l2 and hydrogel
L3 13 L2 AND HYDROGEL

=> d l3 1-13 abs bib

L3 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2003 ACS
AB The antitumor prepns. are **hydrogels** prepd. by impregnation of a collagen-2-hydroxyethyl methacrylate (I) copolymer carrier with camptothecin derivs. A soln. of atelocollagen in an aq. HCl was mixed with an aq. soln. of CPT 11 and I, and the mixt. was further treated with ethylene glycol, an aq. (NH4)2S2O8 soln., and an aq. Na2S2O5 soln. at 37.degree. for 3 h to give a sustained-release **hydrogel**. The **hydrogel** was administered to healthy mice. Plasma level of SN-38 (metabolite of CPT 11) was gradually decreased from 0.5 .mu.g/mL to <0.1 .mu.g/mL over 5 days, while the level after a one-shot injection of an aq. CPT 11 soln. decreased 0.05 .mu.g/mL within a day. The **hydrogel** also showed excellent antitumor effect on mice bearing Ehrlich cells.
AN 1996:50763 CAPLUS
DN 124:97792
TI Sustained-release antitumor **hydrogels** containing camptothecins
IN Kurono, Yukihisa; Kamimura, Kunio; Ikeda, Ken
PA Yakult Honsha Kk, Japan; Daiichi Seiyaku Co
SO Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 07277981	A2	19951024	JP 1994-107359	19940412
PRAI	JP 1994-107359		19940412		

L3 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2003 ACS
AB Implantable collagen-poly(hydroxyethyl methacrylate) (HEMA) **hydrogels** contg. antitumor drugs were prepd. and evaluated for use in controlled drug carrier systems. The drugs used were CPT-11 and SN-38 which were derivs. of camptothecin (CPT). The drugs were released from the **hydrogels** at a const. rate (zero-order release) over about 1 wk. The drugs sited in the plasma of mice were detectable for 5 days after s.c. injection of the **hydrogels** while they were

undetectable at 24 h after the injection of the drug aq. solns. Ehrlich solid tumor was developed by s.c. inoculation of the tumor-cell suspension in the inguinal region of mice. The **hydrogels** demonstrated greatly improved antitumor activity over the drug aq. solns. as evidenced by the gross tumor wt. and the survival time assessments. This was attributed to the controlled and slow release of the drugs from the gels.

AN 1994:586961 CAPLUS
DN 121:186961
TI Application of implantable collagen-poly(hydroxyethyl methacrylate) **hydrogels** containing camptothecin derivative to solid tumor chemotherapy
AU Uemura, Kunio; Kurono, Yukihisa; Ikeda, Ken
CS Faculty Pharmaceutical Sciences, Nagoya City University, Mizuho, 467, Japan
SO Byoin Yakugaku (1994), 20(1), 33-40
CODEN: BYYADW; ISSN: 0389-9098
DT Journal
LA Japanese

L3 ANSWER 3 OF 13 USPATFULL
AB Devices, methods, and compositions for cancer therapy by administration of chemotherapeutic agents and/or inhibitors of membrane efflux systems to the vagina for topical and systemic tumor targets.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 2003:71017 USPATFULL
TI Vaginal delivery of chemotherapeutic agents and inhibitors of membrane efflux systems for cancer therapy
IN Pauletti, Giovanni M., Loveland, OH, UNITED STATES
Liu, James H., Cincinnati, OH, UNITED STATES
Benet, Leslie Z., Belvedere, CA, UNITED STATES
Ritschel, Wolfgang A., Cincinnati, OH, UNITED STATES
PI US 2003049302 A1 20030313
AI US 2002-226667 A1 20020821 (10)
PRAI US 2001-315877P 20010829 (60)
DT Utility
FS APPLICATION
LREP Hana Verny, Howard M. Peters, Allston L. Jones, Susan M. Schmitt, Peters, Verny, Jones & Biksa, 385 Sherman Avenue, Suite 6, Palo Alto, CA, 94306
CLMN Number of Claims: 33
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 1671
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 4 OF 13 USPATFULL
AB The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 2003:37157 USPATFULL
TI Methods for enhancing antibody-induced cell lysis and treating cancer
IN Weiner, George, Iowa City, IA, UNITED STATES
Hartmann, Gunther, Munich, GERMANY, FEDERAL REPUBLIC OF
PI US 2003026801 A1 20030206
AI US 2001-888326 A1 20010622 (9)
PRAI US 2000-213346P 20000622 (60)
DT Utility
FS APPLICATION

LREP Alan W. Steele, Wolf, Greenfield & Sacks, P.C., Federal Reserve Plaza, 600 Atlantic Avenue, Boston, MA, 02210
CLMN Number of Claims: 77
ECL Exemplary Claim: 1
DRWN 6 Drawing Page(s)
LN.CNT 4637
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 5 OF 13 USPATFULL
AB The present invention provides oral dosage forms and compositions for administering antineoplastic agents, such as irinotecan, etoposide, paclitaxel, doxorubicin and vincristine, whose oral effectiveness is limited by pre-systemic and systemic deactivation in the GI tract. Gelling of the gastric retention vehicle composition, and in the case of solid forms concomitant expansion of the composition, retains the antineoplastic drug in the patient's stomach, minimizing pre-systemic and/or systemic deactivation of the drug.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 2002:266329 USPATFULL
TI Compositions and dosage forms for gastric delivery of antineoplastic agents and methods of treatment that use them to inhibit cancer cell proliferation
IN Fleshner-Barak, Moshe, Petach Tikva, ISRAEL
Rosenberger, Vered, Jerusalem, ISRAEL
Lerner, E. Itzhak, Petach Tikva, ISRAEL
PI US 2002147208 A1 20021010
AI US 2001-26573 A1 20011220 (10)
RLI Continuation-in-part of Ser. No. US 2001-887204, filed on 22 Jun 2001, PENDING
PRAI US 2000-213832P 20000623 (60)
US 2001-273428P 20010305 (60)
DT Utility
FS APPLICATION
LREP KENYON & KENYON, ONE BROADWAY, NEW YORK, NY, 10004
CLMN Number of Claims: 79
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1949
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 6 OF 13 USPATFULL
AB The invention relates to the use of pharmacologically valuable pyridyl alkane, pyridyl alkene and/or pyridyl alkine acid amides according to general formula (I) in the treatment of tumors or for immunosuppression. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 2002:239033 USPATFULL
TI Use of pyridyl alkane, pyridyl alkene and/or pyridyl alkine acid amides in the treatment of tumors or for immunosuppression
IN Biedermann, Elfi, Vaterstetten, GERMANY, FEDERAL REPUBLIC OF
Hasmann, Max, Neuried, GERMANY, FEDERAL REPUBLIC OF
Loser, Roland, Feldafing, GERMANY, FEDERAL REPUBLIC OF
Rattel, Benno, Munich, GERMANY, FEDERAL REPUBLIC OF
Reiter, Friedemann, Putzbrunn, GERMANY, FEDERAL REPUBLIC OF
Schein, Barbara, Neufahrn, GERMANY, FEDERAL REPUBLIC OF
Seibel, Klaus, Grafelfing, GERMANY, FEDERAL REPUBLIC OF
Vogt, Klaus, Munich, GERMANY, FEDERAL REPUBLIC OF
PA Klinge Pharma GmbH, Munich, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)
PI US 6451816 B1 20020917

AI US 1998-216482 19981218 (9)
RLI Continuation of Ser. No. WO 1997-EP3244, filed on 20 Jun 1997
DT Utility
FS GRANTED
EXNAM Primary Examiner: Rotman, Alan L.; Assistant Examiner: Desai, Rita
LREP Fitch, Even, Tabin, & Flannery
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 4285
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 7 OF 13 EUROPATFULL COPYRIGHT 2003 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 1087801 EUROPATFULL ED 20020125 EW 200203 FS PS
TIEN TOPOISOMERASE INHIBITORS FOR PREVENTION OF RESTENOSIS.
TIDE TOPOISOMERASE INHIBITOREN ZUR RESTENOSE-PREVENTION.
TIFR INHIBITEURS DE TOPOISOMERASE PERMETTANT DE PREVENIR LA RESTENOSE.
IN EURY, Robert, 20487B Lockwood Drive, Cupertino, CA 95014, US;
ALVARADO, Angelica, 750 Pomeroy Avenue, Santa Clara, CA 95051, US;
POMERANTSEVA, Irina, 8 Pheasantwood Terrace, Wakefield, MA 01880, US;
FROIX, Michael, 433 Woodstock Lane, Mountain View, CA 94040, US
PA Quanam Medical Corporation, 2255 Martin Avenue, Santa Clara, CA 95050, US
PAN 2252862
AG VOSSIUS & PARTNER, Siebertstrasse 4, 81675 Muenchen, DE
AGN 100314
OS BEPB2002006 EP 1087801 B1 0014
SO Wila-EPS-2002-H03-T1
DT Patent
LA Anmeldung in Englisch; Veroeffentlichung in Englisch
DS R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 1087801 B1 20020116
OD 20010404
AI EP 1999-933575 19990624
PRAI US 1998-90764 19980626
RLI WO 99-US14386 990624 INTAKZ
WO 0000238 000106 INTPNR
REP WO 97-31003 A WO 97-33552 A
WO 98-17331 A US 5383928 A
US 5569197 A US 5674192 A
REN FUKUDA, M., NISHIO, K.: "Effects of combinations of CPT-II, paclitaxel and other anticancer agents on human small cell lung cancer cells" CELLULAR PHARMACOLOGY, vol. 3, no. 1, 1996, pages 1-6, XP002120621

L3 ANSWER 8 OF 13 EUROPATFULL COPYRIGHT 2003 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 1012186 EUROPATFULL ED 20020725 EW 200229 FS PS
TIEN USE OF A KGF PROTEIN PRODUCT(S) AND A GLP-2 PROTEIN PRODUCT(S) FOR THE PREPARATION OF A MEDICAMENT.
TIDE VERWENDUNG EINES KGF-PROTEINPRODUKTES UND EINES GLP-2 PROTEINPRODUKTES FUeR DIE HERSTELLUNG EINES MEDIKAMENTES.
TIFR UTILISATION DE PRODUIT(S) PROTEIQUE(S) KGF ET DE PRODUIT(S) PROTEIQUE(S)GLP-2 POUR LA PREPARATION D'UN MEDICAMENT.
IN FARRELL, Catherine, L., 28051 Magic Mountain Lane, Canyon Country, CA 91351, US;

LI, Yue-Sheng, 3565 Birdsong Avenue, Thousand Oaks, CA 91360, US
PA Amgen Inc.,, One Amgen Center Drive, Thousand Oaks, California 91320-1799, US
PAN 923239
AG Gruenecker, Kinkeldey, Stockmair & Schwanhaeusser Anwaltssozietaet, Maximilianstrasse 58, 80538 Muenchen, DE
AGN 100721
OS BEPB2002050 EP 1012186 B1 0119
SO Wila-EPS-2002-H29-T1
DT Patent
LA Anmeldung in Englisch; Veroeffentlichung in Englisch
DS R AT; R BE; R CH; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE; R AL; R LT; R LV; R MK; R RO; R SI
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 1012186 B1 20020717
OD 20000628
AI EP 1997-953157 19971208
PRAI US 1996-32533 19961206
US 1997-62074 19971015
RLI WO 97-US22735 971208 INTAKZ
WO 9824813 980611 INTPNR
REN D J DRUCKER ET AL.: "Induction of intestinal epithelial proliferation by glucagon-2 like peptide" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 93, no. 15, 23 July 1996, WASHINGTON US, pages 7911-7916, XP000602070 BIOLOGICAL ABSTRACTS, vol. 102, no. 7, 1996 Philadelphia, PA, US; abstract no. 96747, M BRAUCHLE ET AL.: "Keratinocyte growth factor is highly overexpressed on inflammatory bowel disease" XP002063839 & AMERICAN JOURNAL OF PATHOLOGY, vol. 149, no. 2, August 1996, pages 521-529,

L3 ANSWER 9 OF 13 EUROPATFULL COPYRIGHT 2003 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 934309 EUROPATFULL ED 20020917 EW 200237 FS PS
TIEN NEW PYRIDYL ALKANE ACID AMIDES AS CYTOSTATICS AND IMMUNOSUPPRESSIVES.
TIDE PYRIDYLALKAN-SAeUREAMIDE ALS CYTOSTATIKA UND IMMUNOSUPRESSIVE ARZNEIMITTEL.
TIFR NOUVEAUX AMIDES A ACIDES PYRIDYL-ALCANE UTILISES COMME CYTOSTATIQUES ET IMMUNOSUPPRESSEURS.
IN BIEDERMANN, Elfi, Zugspitzstrasse 93, D-85591 Vaterstetten, DE;
HASMANN, Max, Lerchenweg 9, D-82061 Neuried, DE;
LOeSER, Roland, Fichtenweg 2, D-82340 Feldafing, DE;
RATTEL, Benno, Eichelhaeherstrasse 3, D-81249 Munich, DE;
REITER, Friedemann, Zugspitzstrasse 36, D-85640 Putzbrunn, DE;
SCHEIN, Barbara, Sudetenweg 4, D-85375 Neufahrn, DE;
SEIBEL, Klaus, Haberlstrasse 9, D-82166 Graefelfing, DE;
VOGT, Klaus, Balanstrasse 63, D-81541 Munich, DE
PA Fujisawa Deutschland GmbH, Berg-am-Laim-Strasse 129, 81673 Muenchen, DE
PAN 283202
AG HOFFMANN - EITLE, Patent- und Rechtsanwaelte Arabellastrasse 4, 81925 Muenchen, DE
AGN 101511
OS BEPB2002065 EP 0934309 B1 0123
SO Wila-EPS-2002-H37-T1
DT Patent
LA Anmeldung in Englisch; Veroeffentlichung in Englisch
DS R AT; R BE; R CH; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 934309 B1 20020911
OD 19990811

AI EP 1997-929240 19970620
PRAI DE 1996-19624704 19960620
RLI WO 97-EP3243 970620 INTAKZ
WO 9748695 971224 INTPNR
REP EP 330026 A EP 343307 A
WO 91-15484 A WO 91-15485 A

L3 ANSWER 10 OF 13 EUROPATFULL COPYRIGHT 2003 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 923570 EUROPATFULL ED 20021007 EW 200239 FS PS
TIEN PYRIDYL ALKENE- AND PYRIDYL ALKINE- ACID AMIDES AS CYTOSTATICS AND IMMUNOSUPPRESSIVES.
TIDE PYRIDYLALKEN- UND PYRIDYLALKIN-SAeUREAMIDE ALS CYTOSTATIKA UND IMMUNOSUPPRESSIVE ARZNEIMITTEL.
TIFR AMIDES PYRIDYL-ALCENE ET PYRIDYL-ALCYNE ACIDES UTILISES COMME CYTOSTATIQUES ET IMMUNOSUPPRESSEURS.
IN BIEDERMANN, Elfi, Zugspitzstrasse 93, D-85591 Vaterstetten, DE;
HASMANN, Max, Lerchenweg 9, D-82061 Neuried, DE;
LOeSER, Roland, Fichtenweg 2, D-82340 Feldafing, DE;
RATTEL, Benno, Eichelhaeherstrasse 3, D-81249 Munich, DE;
REITER, Friedemann, Zugspitzstrasse 36, D-85640 Putzbrunn, DE;
SCHEIN, Barbara, Sudetenweg 4, D-85375 Neufahrn, DE;
SEIBEL, Klaus, Haberlstrasse 9, D-82166 Graefelfing, DE;
VOGT, Klaus, Balanstrasse 63, D-81541 Munich, DE
PA Fujisawa Deutschland GmbH, Berg-am-Laim-Strasse 129, 81673 Muenchen, DE
PAN 283202
AG HOFFMANN - EITLE, Patent- und Rechtsanwaelte Arabellastrasse 4, 81925 Muenchen, DE
AGN 101511
OS BEPB2002069 EP 0923570 B1 0124
SO Wila-EPS-2002-H39-T1
DT Patent
LA Anmeldung in Englisch; Veroeffentlichung in Englisch
DS R AT; R BE; R CH; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 923570 B1 20020925
OD 19990623
AI EP 1997-928261 19970620
PRAI DE 1996-19624659 19960620
RLI WO 97-EP3245 970620 INTAKZ
WO 9748696 971224 INTPNR
REP EP 330026 A EP 343307 A

L3 ANSWER 11 OF 13 EUROPATFULL COPYRIGHT 2003 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 914116 EUROPATFULL ED 20001022 EW 200041 FS PS
TIEN COMPOSITIONS COMPRISING CONJUGATES OF CIS-DOCOSAHEXAENOIC ACID AND TAXOTERE.
TIDE ZUSAMMENSETZUNGEN DIE KONJUGATE VON CIS-DOCOSAHEXAENOIC-SAeURE UND TAXOTERE ENTHALTEN.
TIFR COMPOSITIONS CONTENANT DES CONJUGUES D'ACIDE CIS-DOCOSAHEXANOIQUE ET DE TAXOTERE.
IN BRADLEY, Matthews, O., 4309 Sundown Road, Laytonsville, MD 20882, US;
SHASHOUA, Victor, E., 176 Tappan Street, Brookline, MA 02146, US;
WEBB, Nigel, L., 1101 Green Valley Road, Bryn Mawr, PA 19010, US;
SWINDELL, Charles, S., 613 Schiller Avenue, Merion, PA 19066, US
PA Protarga Inc., 1100 E. Hector Street, Suite 450, Conshohocken, PA 19428,

US
PAN 2438392
AG Jump, Timothy John Simon, Venner Shipley & Co. 20 Little Britain, London EC1A 7DH, GB
AGN 55592
OS BEPB2000050 EP 0914116 B1 0041
SO Wila-EPS-2000-H41-T1
DT Patent
LA Anmeldung in Englisch; Veroeffentlichung in Englisch
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R IE; R IT; R LI; R NL; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 914116 B1 20001011
OD 19990512
AI EP 1997-926722 19970522
PRAI US 1996-651429 19960522
RLI WO 97-US8866 970522 INTAKZ
WO 9744026 971127 INTPNR
REN No relevant documents disclosed

L3 ANSWER 12 OF 13 EUROPATFULL COPYRIGHT 2003 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 912535 EUROPATFULL UP 20020218 EW 200145 FS PS STA R
TIEN CONJUGATES OF CIS-DOCOSAHEXAENOIC ACID AND PACLITAXEL.
TIDE KONJUGATE VON CIS-DOCOSAHEXAENSAeURE UND PACLITAXEL.
TIFR CONJUGUES D'ACIDE CIS-DOCOSAHEXAENOIQUE ET DE PACLITAXEL.
IN BRADLEY, Matthews, O., 4309 Sundown Road, Laytonsville, MD 20882, US; SHASHOUA, Victor, E., 176 Tappan Street, Brookline, MA 02146, US; WEBB, Nigel, L., 1101 Green Valley Road, Bryn Mawr, PA 19010, US; SWINDELL, Charles, S., 613 Schiller Avenue, Merion, PA 19066, US
PA Protarga Inc., 1100 E. Hector Street, Suite 450, Conshohocken, PA 19428, US
PAN 2438392
AG Jump, Timothy John Simon et al., Venner Shipley & Co. 20 Little Britain, London EC1A 7DH, GB
AGN 55592
OS BEPB2001058 EP 0912535 B1 0030
SO Wila-EPS-2001-H45-T1
DT Patent
LA Anmeldung in Englisch; Veroeffentlichung in Englisch
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R IE; R IT; R LI; R NL; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 912535 B1 20011107
OD 19990506
AI EP 1997-930990 19970522
PRAI US 1996-653951 19960522
RLI WO 97-US8792 970522 INTAKZ
WO 9744336 971127 INTPNR
REP WO 89-08453 A WO 90-10443 A
WO 96-04001 A WO 96-21658 A
REN N.F. MAGRI ET AL.: "MODIIFIED TAXOLS, 4." JOURNAL OF NATURAL PRODUCTS, vol. 51, no. 2, 1988, pages 298-306, XP002042959

L3 ANSWER 13 OF 13 EUROPATFULL COPYRIGHT 2003 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 912176 EUROPATFULL ED 20021007 EW 200239 FS PS
TIEN USE OF PYRIDYL ALKANE, PYRIDYL ALKENE AND/OR PYRIDYL ALKINE ACID AMIDES

IN THE TREATMENT OF TUMORS OR FOR IMMUNOSUPPRESSION.

TIDE VERWENDUNG VON PYRIDYL-ALKAN-,PYRIDIYL ALKAN- UND/ODER PYRIDYL-SAeUREN AMIDEN ZUR BEHANDLUNG VON TUMOREN ODER FUeR IMMUNSUPPRESSION.

TIFR UTILISATION D'AMIDES PYRIDYL-ALCANE, PYRIDYL-ALCENE ET/OU PYRIDYL-ALCYNE ACIDES DANS LE TRAITEMENT DES TUMEURS ET POUR L'IMMUNOSUPPRESSION.

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DT Patent

LA Anmeldung in Englisch; Veroeffentlichung in Englisch

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OD			19990506
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PRAI	DE 1996-19624668		19960620
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(54) METHODS OF ADMINISTERING CAMPTOTHECIN COMPOUNDS FOR THE TREATMENT OF CANCER WITH REDUCED SIDE EFFECTS

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(57) ABSTRACT

Methods of administering camptothecin compounds such as irinotecan hydrochloride to reduce a diarrhea side effect and methods of treating cancer and AIDs with camptothecin compounds including administering the camptothecin compounds while maintaining the intestinal lumen and the bile at an alkaline pH.

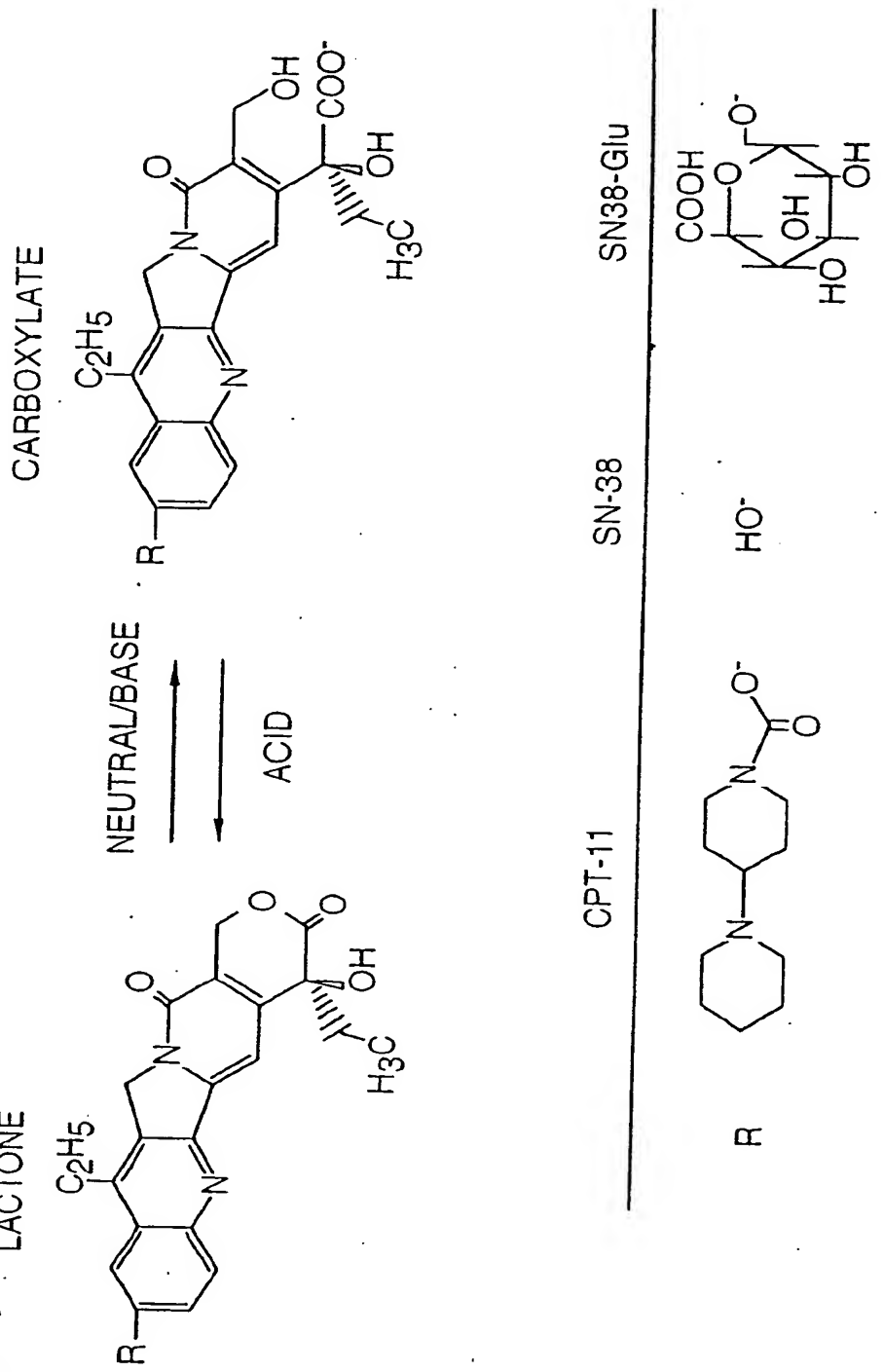

CARBOXYLATE
LACTONE
NEUTRAL/BASE
ACID
SN38-Glu
SN-38
CPT-11
HO-
R

FIG. 1

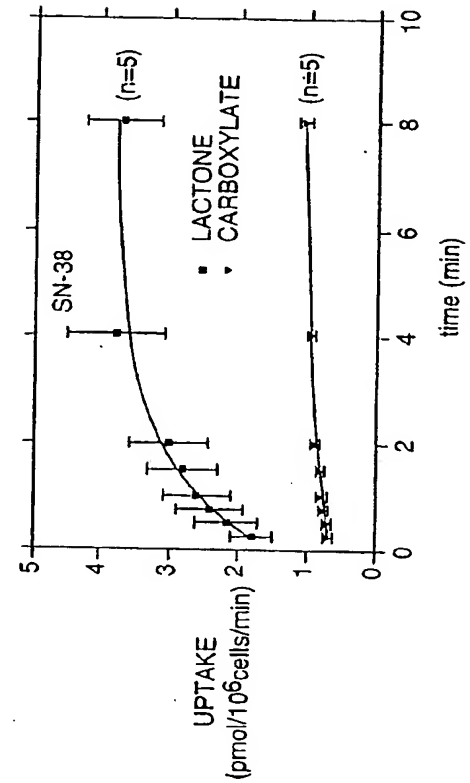

SN-38
LACTONE
CARBOXYLATE
(n=5)
(n=5)
UPTAKE
(pmol/10^6cells/min)
time (min)
0
1
2
3
4
5
0
2
4
6
8
10

FIG. 2B

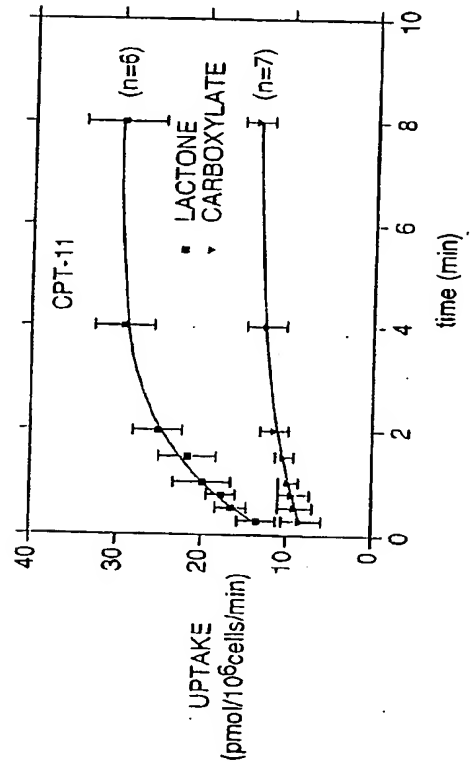

CPT-11
LACTONE
CARBOXYLATE
(n=6)
(n=7)
UPTAKE
(pmol/10^6cells/min)
time (min)
0
10
20
30
40
0
2
4
6
8
10

FIG. 2A

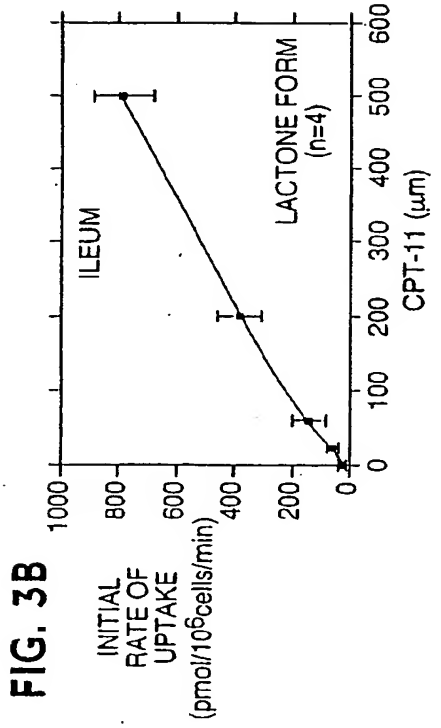


FIG. 3B

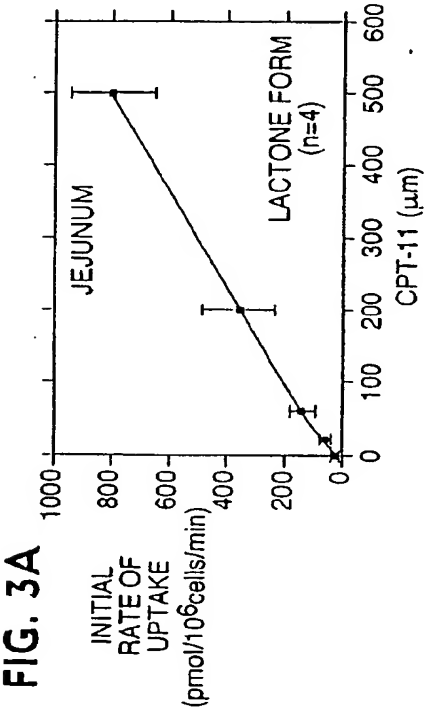


FIG. 3A

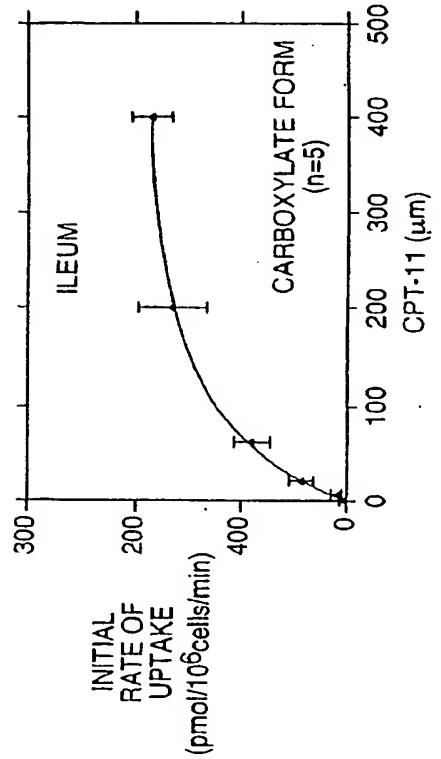


FIG. 3D

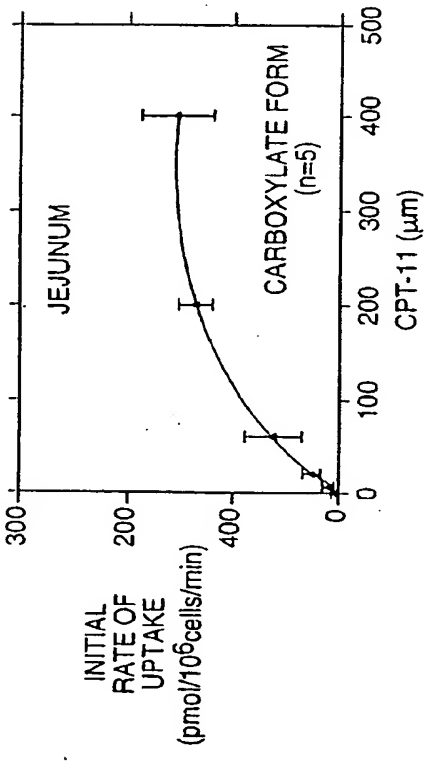


FIG. 3C

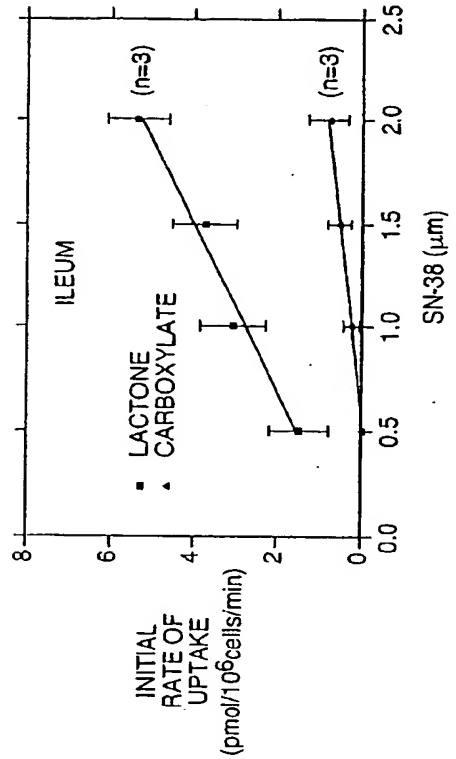

ILEUM
LACTONE
CARBOXYLATE
(n=3)
(n=3)
INITIAL RATE OF UPTAKE (pmol/10^6cells/min)
SN-38 (μm)
0
2
4
6
8
0.0
0.5
1.0
1.5
2.0
2.5

FIG. 4B

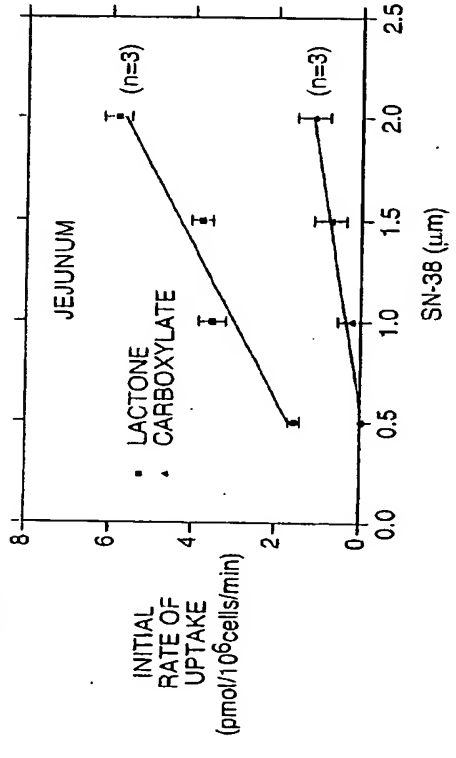

JEJUNUM
LACTONE
CARBOXYLATE
(n=3)
(n=3)
INITIAL RATE OF UPTAKE (pmol/10^6cells/min)
SN-38 (μm)
0
2
4
6
8
0.0
0.5
1.0
1.5
2.0
2.5

FIG. 4A

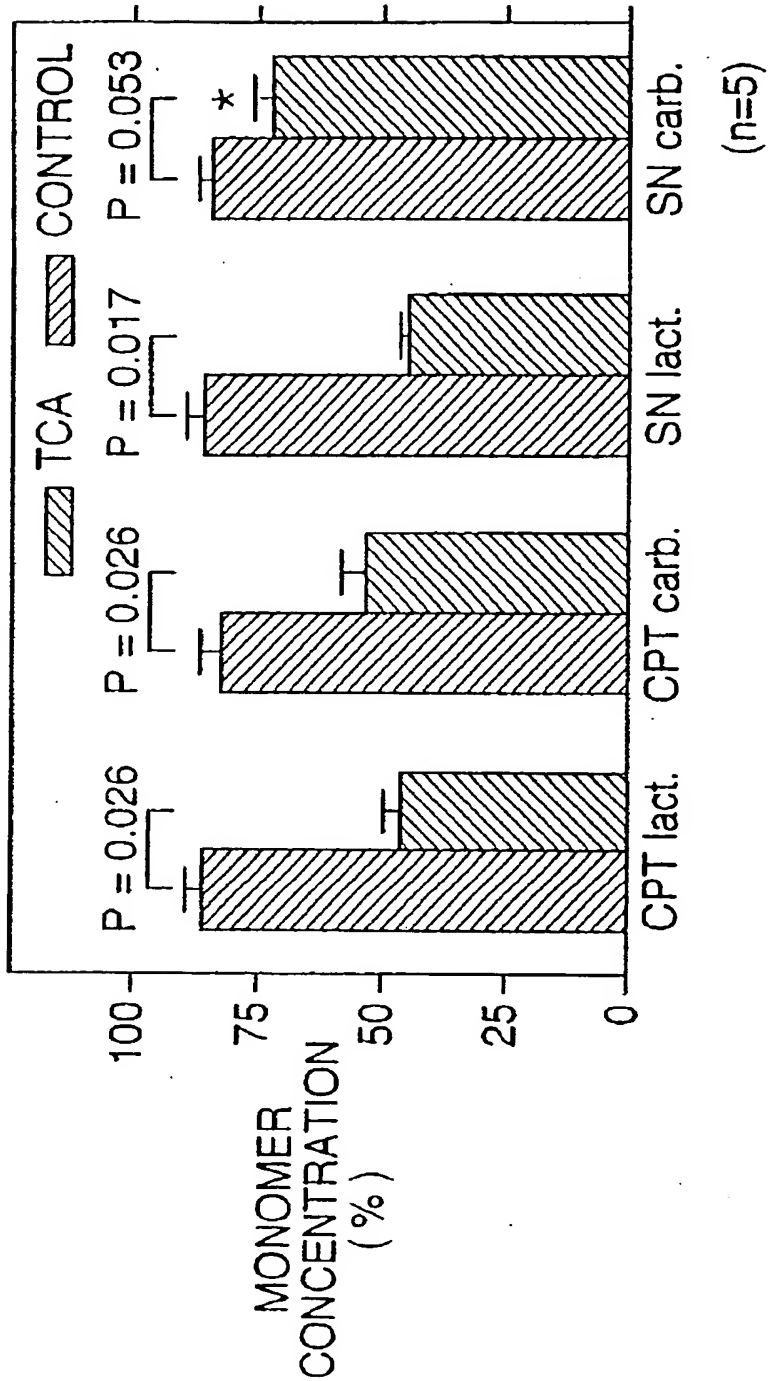

TCA
CONTROL
P = 0.026
P = 0.026
P = 0.017
P = 0.053
*
CPT lact.
CPT carb.
SN lact.
SN carb.
(n=5)
MONOMER CONCENTRATION (%)
100
75
50
25
0

FIG. 5

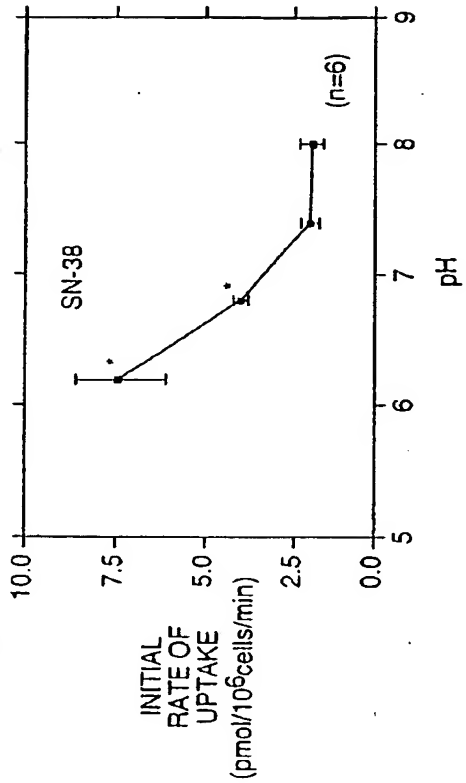

SN-38
(n=6)
INITIAL RATE OF UPTAKE (pmol/10^6cells/min)
10.0
7.5
5.0
2.5
0.0
5
6
7
8
9
pH

FIG. 6B

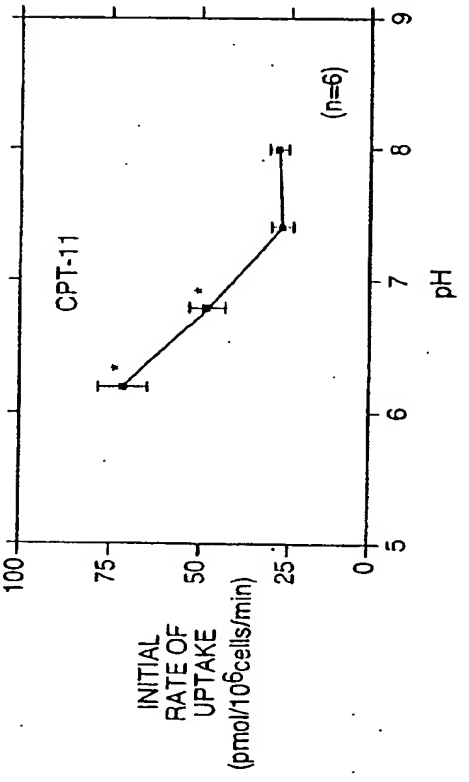

CPT-11
(n=6)
INITIAL RATE OF UPTAKE (pmol/10^6cells/min)
100
75
50
25
0
5
6
7
8
9
pH

FIG. 6A

FIG. 7

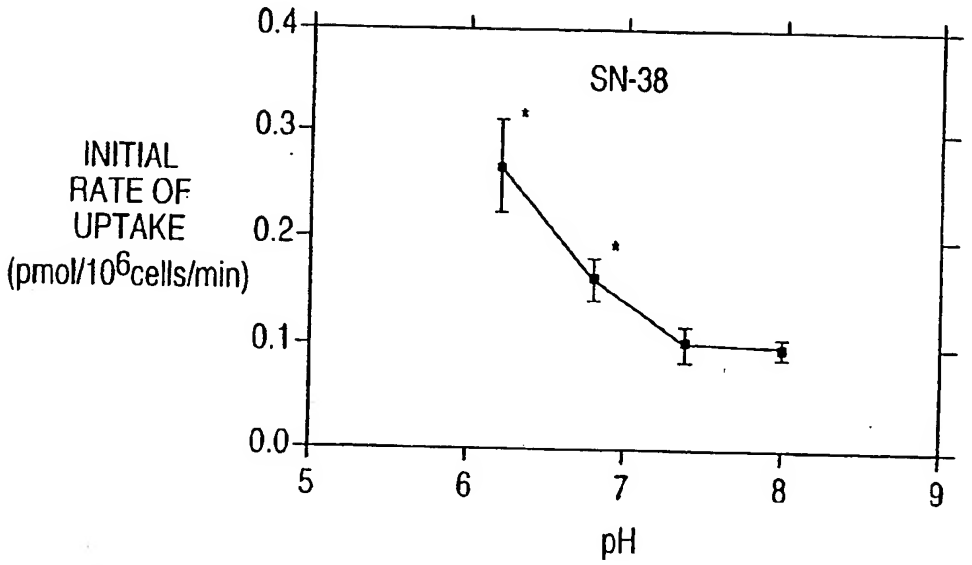
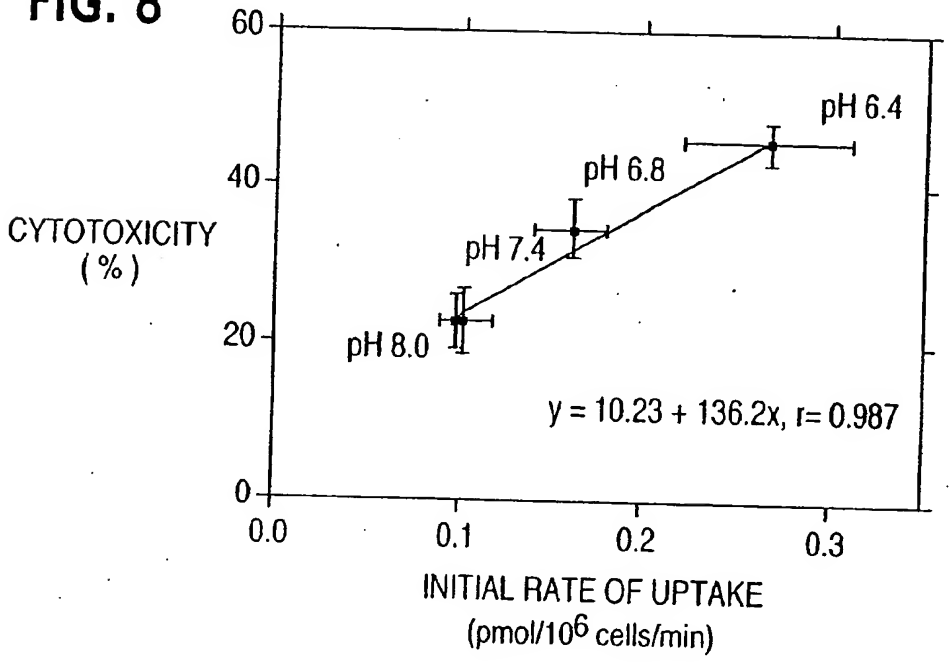

SN-38
INITIAL RATE OF UPTAKE (pmol/10^6cells/min)
0.4
0.3
0.2
0.1
0.0
5
6
7
8
9
pH

FIG. 8


CYTOTOXICITY (%)
60
40
20
0
pH 6.4
pH 6.8
pH 7.4
pH 8.0
y = 10.23 + 136.2x, r= 0.987
0.0
0.1
0.2
0.3
INITIAL RATE OF UPTAKE (pmol/10^6 cells/min)

METHODS OF ADMINISTERING CAMPTOTHECIN COMPOUNDS FOR THE TREATMENT OF CANCER WITH REDUCED SIDE EFFECTS

FIELD OF THE INVENTION

[0001] The present invention relates to camptothecin compounds, in particular, irinotecan hydrochloride composition formulations, and methods of administering camptothecin compounds such as irinotecan hydrochloride for the treatment of cancer and AIDS, with reduced side effects.

BACKGROUND OF THE INVENTION

[0002] Camptothecin is a quinoline-based alkaloid found in the barks of the Chinese Camptotheca tree and the Asian nothapodytes tree. It is a close chemical relative to aminocamptothecin, CPT-11 (irinotecan), DX-8951F and topotecan. These compounds are useful in treating breast cancers, ovarian cancer, colon cancer, malignant melanoma, small cell lung cancer, thyroid cancers, lymphomas and leukemias. These compounds are also used for the treatment of AIDS.

[0003] Irinotecan hydrochloride (CPT-11) (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy] 1H-pyrano [3', 4':6,7] indolizino,[1,2-b]quinoline-3,14(4 h,12H)dione hydrochloride, has a novel mechanism of antitumor activity, namely the inhibition of DNA topoisomerase I. Topoisomer-ases are the enzymes which wind and unwind the DNA that makes up the chromosomes. As the chromosomes must be unwound to make proteins, camptothecin compounds keep the chromosomes wound tight so that they cannot make proteins. Because cancer cells grow at a much faster rate than normal cells, they are more vulnerable to topoisomerase inhibition than normal cells.

[0004] CPT-11 has shown effective antitumor activity clinically (2, 3), and, recently, a survival benefit by CPT-11 was shown in colorectal cancer. However, it has major toxicities of leukopenia and diarrhea in clinical practice. The clinical use of CPT-11 at higher dosages was associated with an unexpected and significant incidence of diarrhea (4, 6, 7, 12), and diarrhea is now recognized as a dose-limiting toxicity of this drug (4-7). Although many pharmacokinetic analyses, which have shown a great interpatient variability, have been made to predict the incidence of diarrhea, there are somewhat conflicting results (8-11).

[0005] CPT-11 and its metabolites, SN-38 and SN-38-Glu, were detected in not only human plasma but also human bile. Of the three compounds, SN-38 has strong cytotoxicity, SN-38-Glu is a deactivated, glucuronidated form of SN-38, and CPT-11 has much less cytotoxicity compared to SN-38. These compounds have an α-hydroxy-3-lactone ring, which undergoes reversible hydrolysis at a rate that depends mainly on pH (15, 16, 17). At more than physiological pH, the lactone form is unstable and the equilibrium favors hydrolysis to open the lactone ring and yield the carboxylate form. Under acidic conditions, the reverse reaction, with formation of the lactone, is favored. Similar reactions also occur with CPT-11 and SN-38-Glu.

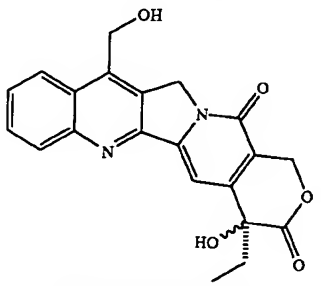
[0006] From several reports, it is considered that major metabolic pathways in human are as follows; CPT-11 is hydrolyzed by carboxylesterase of mainly liver origin to the active metabolite, 7-ethyl-10-hydroxy-camptothecin (SN-38). Some of SN-38 undergoes subsequent conjugation by the hepatic enzyme, UDP-glucuronyltransferase, to SN-38 β-glucuronide (SN-38-Glu), and is excreted into bile along with the other components, CPT-11 and SN-38 (13, 14). The three compounds are believed to be reabsorbed by intestinal cells to enter the enterohepatic circulation. Recently, it has been found that hepatic cytochrome P-450 3A enzymes metabolize CPT-11 to 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin, which has 500-fold weaker antitumor activity than SN-38 (Rivory et al., 1996b; Haaz et al., 1997). CPT-11, SN-38 and SN38-Glu have an α-hydroxy-3-lactone ring, which undergoes reversible hydrolysis at a rate which is mainly pH-dependent (Fassberg et al., 1992). At physiological pH and higher, the lactone form is unstable and the equilibrium favors hydrolysis to open the lactone ring and yield the carboxylate form. Under acidic conditions, lactone-carboxylate interconversion is shifted toward the lactone form. CPT-11, SN-38 and SN38-Glu are excreted into bile and along with it are released into the small intestinal lumen (Atsumi et al., 1991; Lokiec et al., 1995; Chu et al., 1997a, b). Furthermore, although minor (Atsumi et al 1995), an additional pathway involves direct transport of CPT-11 and its metabolites from serum to lumen across the intestinal epithelial cells. Once in the intestine, SN38-Glu can be deconjugated in the cecum and colon to SN-38 by bacterial β-glucuronidase (Takatsuna et al., 1996). CPT-11, SN-38 and SN38-Glu are believed to be reabsorbed to a certain extent by intestinal cells and to enter the enterohepatic circulation.

[0007] To date, there is little information about the intestinal uptake and transport mechanism of CPT-11 and its derivatives. This knowledge is a critical step in the understanding of the mechanism by which CPT-11 induces diarrhea. In the present study, the uptake of CPT-11 and SN-38 by intestinal epithelial cells was estimated and correlated to their respective effect on cell toxicity.

[0008] The structure of several camptothecin derivatives are known.

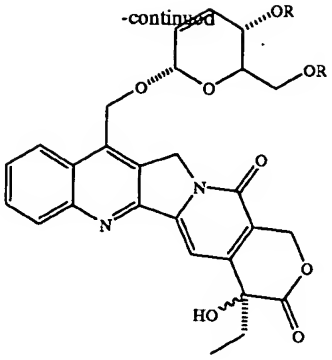
Glycosylated Analogs of 7-Hydroxymethylcamptothecin

HAR8

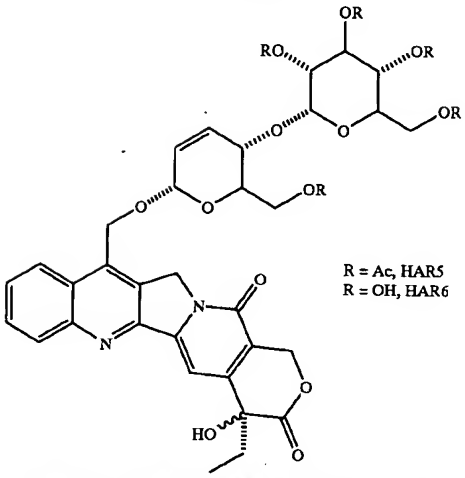


7-hydroxymethyl camptothecin

-continued

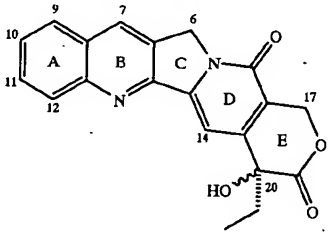


R = Ac, HAR4
R = OH, HAR7

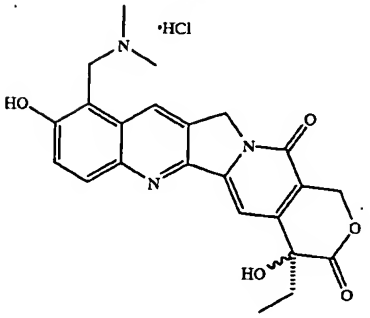


R = Ac, HAR5
R = OH, HAR6

Camptothecin and Analogs Currently in Clinical Development



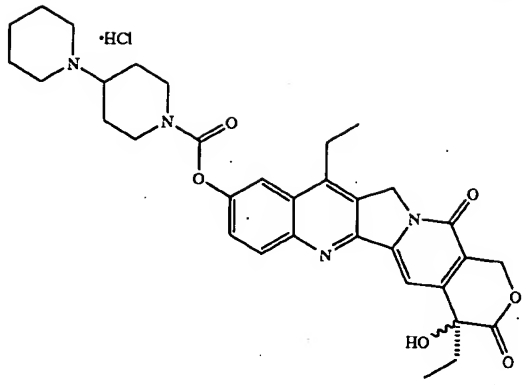
Camptothecin



Topotecan

-continued

CPT-11



[0009] In addition, U.S. Pat. No. 5,552,154 discloses that camptothecin (CPT) and derivatives thereof of the closed lactone ring form are administered intramuscularly or orally. In such cases, it was possible to obtain total remissions of a vast spectrum of human cancers without the toxicity observed previously with CPT Na+. The derivatives of CPT used were 9-Amino-20 (S)-Camptothecin (9AC). 9-Nitro-20(S)-Camptothecin ($9NO_2$).

[0010] U.S. Pat. No. 5,468,754 describes that CPT 11 and other camptothecin derivatives undergo an alkaline; pH-dependent hydrolysis of the E-ring lactone. The slow reaction kinetics allow one to assess whether both lactone and non-lactone forms of the drug stabilize the topoisomerase-cleaved DNA complex. Studies indicate that only the closed lactone form of camptothecin helps stabilize the cleavable complex. Therefore, the patent recommends that pH levels of below 7 be used to allow the lactone form of camptothecin to predominate. The patent suggests the administration of the compounds with a pharmaceutically acceptable acid.

[0011] U.S. Pat. No. 5,447,936 describes that the HECPT form of the drug is more effective in inhibiting topoisomerase-I in an acidic environment, than in cells having higher intracellular pH levels. The patent describes the administration of the drug with an acid which is an organic carboxylic acid such as citric acid.

[0012] U.S. Pat. No. 5,225,404 describes the administration of a camptothecin compound with water-based solvents for water-soluble compounds such as normal saline or phosphate buffered saline solutions. The patent indicates that signs of diarrhea and cystitis were prevented and no overall toxicity was obtained.

[0013] U.S. Pat. No. 5,637,770 describes the creation of a hexacyclic compound obtained by the addition of a water-soluble ring to camptothecin, which had superior characteristics to camptothecin. U.S. Pat. No. 5,633,016 describes a combination cancer therapy including administering an effective amount of topotecan with cisplatin.

[0014] U.S. Pat. No. 5,633,260 discloses a 7-11-substituted camptothecin derivative. The patent also describes that maintaining an acidic pH (3 to 4) in the formulation is important to reduce the slow conversion of 11,7-HECPT

lactones with the E-ring-hydrolyzed carboxylate which occurs at physiological pH. This patent prescribes regulated dosages to eliminate toxicity of the compound.

[0015] U.S. Pat. No. 5,652,244 describes a method of treating human carcinoma with camptothecin derivatives. U.S. Pat. No. 5,658,920 describes a hexacyclic compound derivative of camptothecin.

[0016] U.S. Pat. No. 5,597,829 discloses that CPT is excreted unchanged by the kidneys, although a large percentage of the drug administered cannot be accounted for in the urine. The patent suggests that enhanced renal excretion of the carboxylate form of CPT occurs when exposed to a pH lower than 5. Therefore, it is recommended the administration of the drug to assure an acidic pH value by administering the compound with organic carboxylic acids.

[0017] U.S. Pat. No. 5,674,874 describes the pharmacologic conversion of CPT 11 to HECPT. The patent describes administration of the compound in sufficient quantities to maintain the pH of the formulation from about 2 to about 6 with the administration of a pharmaceutically acceptable acid.

[0018] Cancer Investigation, Volume 14, Supplement 1, No. 31, describes the use of irinotecan (CPT 11) to treat colon cancer and non-small cellular lung cancer. The publication confirms the incidence of grade 4 diarrhea associated with administration of CPT 11 dropped from 17% to 5% following adoption of an aggressive loperimide therapy.

[0019] Irinotecan Approved for Advance Colorectal Cancer, Med. Sci. Bull 1996; Volume 18, No. 12, describes that diarrhea is a common side effect of irinotecan administration.

[0020] Journal of the National Cancer Institute, September 4, 1996, Vol. 88, No. 17, suggests that excessive production of sulphomucin in the cecum could be the major cause of CPT-11-induced diarrhea.

[0021] The Camptosar Patient Management Guidelines suggest avoiding the diarrhea side effect of camptosar by administering loperimides and gatorade.

[0022] The present invention overcomes one of the major side effects, diarrhea, associated with administration of camptothecin compounds, in particular irinotecan hydrochloride. This is one of the major deficiencies in the prior art in delivering irinotecan hydrochloride for the treatment of tumors. The present invention overcomes the diarrhea side effect associated with the administration of irinotecan hydrochloride and its related compounds.

SUMMARY OF THE INVENTION

[0023] The present invention provide for methods of administering camptothecin compounds which are cleared through the liver, preferably irinotecan hydrochloride and its derivatives.

[0024] The invention provides a method of inhibiting a diarrhea side effect of camptothecin compounds cleared by the liver, including but not limited to, irinotecan hydrochloride (CPT-11), SN38-Glu, and SN-38 comprising administering irinotecan hydrochloride while the intestinal lumen is maintained an alkaline pH.

[0025] The invention also provides a method of treating cancer comprising administering camptothecin compounds such as irinotecan hydrochloride while maintaining the intestinal lumen at an alkaline pH.

[0026] In a preferred embodiment the cancer is selected from, but not limited to, breast cancer, ovarian cancer, colon cancer, malignant melanoma, small cell lung cancer, thyroid cancers, lymphomas and leukemias.

[0027] In another embodiment the invention provides a method of treating AIDS comprising administering irinotecan hydrochloride while maintaining the intestinal lumen at an alkaline pH.

[0028] The invention advantageously provides a method of administering a camptothecin compound such as irinotecan hydrochloride (CPT-11) intravenously comprising prior to or simultaneously administering said camptothecin compound, orally administering a bicarbonate and alkaline H_2O.

[0029] The invention provides a method of administering a camptothecin compound such as irinotecan hydrochloride (CPT-11) intravenously comprising prior to or simultaneously administering said camptothecin compound, orally administering a composition comprising borbic acid.

[0030] The invention also provides for a method of administering a camptothecin compound comprising prior to or simultaneously administering said camptothecin compound, orally administering a composition comprising urso-deoxycholic acid.

[0031] Throughout the present specification where compositions, kits, and methods are described as including or comprising specific components, it is contemplated by the inventors that compositions of the present invention also consist essentially of or consist of the recited components.

[0032] The above and other objects of the invention will become readily apparent to those of skill in the relevant art from the following detailed description and figures, wherein only the preferred embodiments of the invention are shown and described, simply by way of illustration of the best mode of carrying out the invention. As is readily recognized the invention is capable of modifications within the skill of the relevant art without departing from the spirit and scope of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0033] **FIG. 1** shows structures of CPT-11, SN-38 and SN-38-glucuronide (SN-38-GLU): Lactone forms of CPT-11 and SN-38 are non-ion charged, and carboxylate forms of CPT-11 and SN-38 are anions. Not only carboxylate form of SN-38-Glu but also its lactone form, which possesses an additional carboxyl group in its glucuronide moiety, is an anion. The reversible conversion between lactone and carboxylate forms is pH driven.

[0034] **FIGS. 2A and 2B** show the time course of CPT-11 and Sn-38 uptake by isolated intestinal cells: The uptake of [^{14}C] CPT-11 (20 μM) and [^{14}C] SN-38 (2 μM) in lactone and carboxylate form, respectively, by isolated intestinal cells from jejunum was measured as a function of time. At time 0, the respective agent was added to the intestinal cell suspension maintained at 37° C. under permanent shaking. At 15, 30, 45, 60, 90, 120, 240 and 480 sec, aliquots of cell

suspension were removed, and processed as described in Materials and Methods. The results shown are mean ±SE of n experiments.

[0035] FIGS. 3A, 3B, 3C and 3D show the relationship between initial rate of uptake of CPT-11 and its concentration: The initial uptake rate was determined from the linear slope of the cellular uptake over the initial 90 sec incubation period. The data were fitted by least-square nonlinear regression analysis using the equation $V=(V_{max} S)/(K_m+S)+K_d S$ where V represents the initial rate of uptake, V_{max} is the maximum rate of uptake, K_m is the apparent Michaelis constant, K_d is the rate of diffusion and S is the concentration of CPT-11.

[0036] FIGS. 4A and 4B show the relationship between initial rate of uptake of SN-38 and its concentration. The initial uptake rate was determined as described in legend of FIG. 3 and in Materials and Methods. The data were fitted by least-square linear regression. Because of limited solubility, only concentrations of SN-38 up to 2 μM were investigated.

[0037] FIG. 5 shows the effect of taurocholate (TCA) on respective CPT-11 and SN-38 micelle formation: [^{14}C] CPT-11 (20 μM) and [^{14}C] SN-38 (2 μM) were stored overnight in Hank's solution in the presence of absence of TCA (20 mM). Monomers were separated from micellar aggregates by ultrafiltration through a 1000-molecular weight cut-off membrane (YM1) as described in Materials and Methods. Values are the monomeric forms of the indicated metabolites, expressed as a percentage (%) of the concentration of the initial solution before ultrafiltration. Comparison between TCA and control was estimated by Mann-Whitney test. (*): Sn-38 carboxylate is significantly different from the other agents tested in the presence of TCA (Kruskal-Wallis test: p=0.023, Student-Newman-Keuls method, p<0.05). Abbreviations used: CPT lactone (CPT lact.); CPT carboxylate (CPT carb.); SN-38 lactone (SN lact.); and SN-38 carboxylate (SN carb.).

[0038] FIGS. 6A and 6B show the effect of pH on the initial rate of uptake of CPT-11 and SN-38: [^{14}C] CPT-11 (20 μM) and [^{14}C] SN-38 (2 μM) were dissolved in PBS at pH 6.2, 6.8, 7.4 and 8.0 and stored overnight. By adding the drugs to Hank's solution containing intestinal cells from whole small-intestine, uptake studies were performed. The difference in the initial uptake rate by pH was analyzed by Kruskal-Wallis test (p<0.001 and p<0.001 for CPT-11 and SN-38, respectively) and Student-Newman-Keuls method (*p<0.05).

[0039] FIG. 7 shows the effect of pH on the initial uptake rate of HT29 cells. [^{14}C]SN-38 (2 μM) were dissolved in PBS at pH 6.2, 6.8, 7.4 and 8.0 overnight. The uptake study was 2p initiated by adding the compounds to Hanks' solution containing HT29 cells. The comparative initial rate of uptake as function of pH was analyzed by Kruskal-Wallis test (p<0.001) and Dunn's method (*p<0.05).

[0040] FIG. 8 shows the relationship between the initial uptake rate and the cytotoxicity of SN-38. Using HT29 cells, the effect of physiological pH on the initial uptake rate of 2 μM [^{14}C]SN-38 was estimated as described in legend of FIG. 3. The 0.4 μM SN-38-induced cytotoxicity in HT29 cells was studied by the described MTT assay. The relationship between the initial rate of uptake and the cytotoxicity of SN-38 was plotted by a simple least-squares regression method.

DESCRIPTION OF THE INVENTION

[0041] Knowledge of the cellular transport mechanism of camptothecin compounds such as CPT-11 and its metabolites by the intestine is a critical step in the understanding of the mechanism by which camptothecin compounds, such as CPT-11, induce diarrhea and its great interpatient variability in pharmacokinetics. The inventors reviewed the uptake of several camptothecin compounds, CPT-11 and SN-38, by intestinal epithelial cells. The results provide for the new design of an approach to prevent diarrhea and large interpatient variability in pharmacokinetics in clinical practice of the treatment of cancer and tumors with irinotecan hydrochloride and its related compounds.

[0042] The invention provides a method of inhibiting a diarrhea side effect of camptothecin compounds such as irinotecan hydrochloride (CPT-11), SN-38-Glu, SN-38 and its derivatives comprising administering irinotecan hydrochloride while maintaining the bile and/or intestinal lumen at an alkaline pH. In a preferred embodiment the intestinal lumen is maintained at an alkaline pH by administration of bicarbonate and alkaline H_2O. The amount of bicarbonate and alkaline pH is suitable to reduce the uptake of the camptothecin compound and thus reduce the cytotoxic side effects including a diarrhea side effect. The camptothecin compound or irinotecan hydrochloride may be administered intravenously, orally or intramuscularly. The method of the invention inhibits the reabsorption and decreases the lactone uptake of CPT-11 and SN-38 by the intestines and thus reduces the diarrhea side effect associated with camptothecin compounds such as irinotecan hydrochloride.

[0043] The invention also provides a method of treating cancer comprising administering irinotecan hydrochloride and its derivatives or mixtures thereof, while maintaining the intestinal lumen at an alkaline pH. In a preferred embodiment the cancer is selected from the group consisting of, but not limited to breast cancer, ovarian cancer, colon cancer, malignant melanoma, small cell lung cancer, thyroid cancers, lymphomas and leukemias. The alkaline pH may be a pH from about 7 to about 10. In an alternative embodiment the cancer is treated by administering a compound selected from 7-hydroxymethyl camptothecin, irinotecan hydrochloride, aminocamptothecin, DX-8951F, SN-38, HAR4, HAR5, HAR6, HAR7, HAR8 and topotecan, while maintaining the intestinal lumen at an alkaline pH.

[0044] The invention advantageously provides for a method of treating AIDS comprising administering irinotecan hydrochloride or its derivatives while maintaining the intestinal lumen at an alkaline pH.

[0045] A pharmaceutical composition and kit including irinotecan hydrochloride (CPT-11) administered in combination with a bicarbonate selected from sodium bicarbonate, magnesium bicarbonate and potassium bicarbonate. Alternatively irinotecan hydrochloride (CPT-11) may be administered in combination with a composition comprising borbic acid. This chemical has been used in buffers composition, such as the Britton-Robinson buffer and has a strong alkalinic buffering action.

[0046] The invention also provides for a method of administering a camptothecin compound comprising prior to or simultaneously administering said camptothecin compound, orally administering a composition comprising urso-deoxy-

cholic acid. This composition may optionally be administered with bicarbonate. It is believed that urso-deoxycholic acid stimulates bicarbonate secretion into bile.

[0047] The following example shows the ability to reduce the diarrhea side effect of irinotecan hydrochloride compounds in accordance with the method of the invention.

EXAMPLE

[0048] Drugs and Animals

[0049] ^{14}C-Labeled SN-38 (3.68 MBg/mg) and ^{14}C-Labeled CPT-11 (1.47 MBq/mg) were kindly donated by Daiichi Pharmaceutical Co., Ltd. Tokyo, Japan). Non-labeled CPT-11, SN-38, and SN-38-Glu were supplied by Yakult Honsha Co., Ltd. Tokyo, Japan). ^{14}C-labeled SN-38 was dissolved in DMSO at a final concentration 2 μM because it was very hydrophobic and poorly soluble in water. DMSO at 2% was confirmed to have no effect on the initial uptake of labeled CPT-11 and SN-38. The other drugs were dissolved in distilled water. The lactone and carboxylate forms of ^{14}C-labeled CPT-11 and SN-38 were produced by dissolving the compound overnight in 50 mM phosphate buffer at pH 6. or 9, respectively. DNP-SG was made from glutathione and CDNB (1-chloro-2,4-dinitro benzene) chemically. All other reagents were of analytical grade. Adult male Golden Syrian hamsters (6-8 weeks age), whose model presents a bile acid profile similar to that observed in human (28), were used.

[0050] Preparation of Intestinal Cells

[0051] Intestinal cells were isolated as previously described (28, 29). Briefly, male hamsters were anesthetized with sodium pentobarbital (Nembutol 70 mg/kg body weight). The entire intestine was removed. The intestinal lumen was washed with 37° C. Hank's solution. Sacs of the ileum (12.5 cm from cecum) and jejunum (remaining small intestine) were rinsed, as well as the intestinal sacs of the anal site of small intestine (12.5 cm from cecum) and oral site (the other small intestine). The sacs were rinsed with oxygenated buffer solution containing sodium citrate (96 mM NaCl, 1.5 mM KCl, 5.6 mM KH_2PO_4, 27 mM sodium citrate, pH 7.3), and incubated for 10 min in the same buffer at 37° C. The sacs were then emptied, filled with oxygenated buffer solution containing EDTA (140 mM NaCl, 16 mM Na_2HPO_4, 2 mM EDTA, 0.5 mM dithiothreitol, pH 7.3), incubated for 10 min at 37° C. Then each sac was placed onto a petri dish and gently vortexed for 1 min. The buffer containing intestinal cells was recovered in 50 mL of Hanks' solution, washed twice and adjusted at 10^6 cells/ml in Hanks' medium (cellular stock solution containing 0.5% bovine serum albumin, pH 7.4)..

[0052] Determination of the Cellular Uptake of ^{14}C-labeled CPT-11 and SN-38, respectively

[0053] Uptake of ^{14}C-labeled CPT-11 and SN-38 was measured by rapid vacuum filtration assay (28, 29). The cellular suspension of 0.95 ml was incubated for 15 min in a 37° C. water bath with stirring. Uptake was started by the addition of 0.05 ml PBS (at pH 3 or 9) containing labeled SN-38 or CPT-11 at 37° C. At various time intervals, 100 μL, sample aliquots were diluted into 3 mL of Hank's medium at 4° C. to stop the uptake. The stop solution containing the cells was filtered through a glass microfiber filter (Glass Fiber Filter Circles G4, Fisherbrand, Pa.) under vacuum (20 psi). The cells were washed once with 5 mL of 0.5% bovine serum albumin-containing Hanks' medium (4° C.) and once with 20 mL of Hanks' solution (4° C.). The filters were placed in a vial containing 4 mL of scintillation liquid (Ultra Gold, Packard, Conn.) and the radioactivity was counted in a β scintillation counter (LS3801, Beckman, Md.).

[0054] The effect of the metabolic inhibitor, 2,4 dinitrophenol (1 mM), was studied by adding this agent to the cells 3 min prior to either ^{14}C-CPT-11 or ^{14}C-SN-38 (2 μM). The effect of 20 mM of taurocholic acid (TCA) on the uptake of both CPT-11 and SN-38 was investigated following overnight incubation of ^{14}C-CPT-11 (20 μM) and ^{14}C-SN-38 (2 μM) in Hank's solution, at pH 7.4 and in the presence and absence of TCA. The effect of 200 μM of DNP-SG or SN-38-Glu was also studied by adding these agents to the cell preparation 7 min prior to either ^{14}C-CPT-11 (20 μM) and ^{14}C-SN-38 (2 μM).

[0055] The effect of physiologic pH on the initial intestinal uptake rate of CPT-11 and SN-38 was investigated following overnight incubation of ^{14}C-CPT-11 (20 μM) and ^{14}C-SN-38 (2 μM) in phosphate buffered saline at pH 6.2, 6.8, 7.4 and 8, respectively.

[0056] Estimation of Micelle Formation

[0057] To assess whether or not CPT-11 and SN-38 form micelles, these agents were incubated overnight at pH 4 and 9 in a calcium and magnesium free Hank's solution containing 10 mM TCA. The respective solution was filtered through a 1000-molecular weight cut-off membrane YM1 (Diaflo, Amicon, Mass.) at a steady speed of 0.04 ml/min. Once the filtration was stopped, the radioactivity in the initial solution as well as in the filtrate and in the retained solution after filtration was determined as described previously.

[0058] Cytotoxicity Assay

[0059] Rapid colorimetric assay for mitochondrial dehydrogenase activity was modified and used for the estimation of cytotoxicity of SN-38 (Mosmann, 1983). Briefly, HT29 cells were seeded into a 12-well plate (Falcon-3043, Lincoln Park, N.J.), and, after 48 h, SN-38 (0.4 μM) at pH 6.2, 6.8, 7.4 and 8.0 was added. After 24 h-exposure, the cells were washed twice, and subjected to a drug-free incubation for 24 h. Then, the cells were incubated with 0.5 mg/ml 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) for 4 h, and the blue formazan crystals were solubilized by addition of 10% n-dodecylsulfate sodium salt (SDS) in 0.1N HCl and overnight incubation. The formation of the blue formazan compound is spectrophotometrically determined at 560 nm (Ultraspec 4050, LKB, Bromma, Sweden).

[0060] Statistical Analysis

[0061] The initial rate of uptake of CPT-11 or SN-38 was derived from the linear regression analysis of the respective regression line obtained from the plot of the uptake as a function of time. The initial rates of uptake were plotted against the corresponding concentration. The data were fitted by least-squares nonlinear regression analysis (SigmaStat, Jandel Scientific, Calif.), using the equation $V=(V_{max}\cdot S)/(K_m+S)+K_d\cdot S$ where V represents the initial rate of uptake. V_{max} is the maximum rate of uptake, K_m is

the apparent Michaelis constant, K_d is the rate of diffusion and S is the concentration of CPT-11 or SN-38.

[0062] Comparisons between two groups were evaluated by the Mann-Whitney Rank Sum Test. Statistical significance of differences among more than two groups was determined by Kruskal-Wallis One Way Analysis of Variance on Ranks, then multiple comparisons versus control group were performed by Dunn's Method. The correlation between the initial rate of uptake and the cytotoxicity of SN-38 was plotted by a simple least-squares regression method.

[0063] Uptake of CPT-11 and SN-38 Lactone and Carboxylate, Respectively by Intestinal Cells

[0064] The time-dependent uptake of 20 μM ^{14}C-CPT-11 and 2 μM ^{14}C-SN-38 in both lactone and carboxylate forms by isolated jejunal cells is shown in **FIG. 2**. The extrapolation of the uptake value at time 0 yields a positive intercept, indicative of non-specific binding, such as adsorption to labeled agents on the cell surface. The respective uptake of the lactone and carboxylate forms of both CPT-11 and SN-38 was linear for up to 90 sec. Therefore, the initial uptake rate was determined by linear regression fit of the uptake over the initial period of time. Comparison of the uptake rate between the lactone and carboxylate form of the respective agent clearly showed a more rapid uptake of both CPT-11 and SN-38 lactone, as compared to carboxylate form (**FIG. 2**).

[0065] Table 1 summarizes the respective initial uptake rate of 20 μM ^{14}C-CPT-11 and 2 μM ^{14}C-SN-38 by jejunal and ileal cells. CPT-11 and SN-38 lactone were more rapidly taken up than their carboxylate forms in cells from both intestinal regions but without significant differences between jejunal and ileal cells.

[0066] Transport System of CPT-11 and SN-38 Lactone and Carboxylate

[0067] The respective initial uptake rate of CPT-11 lactone and carboxylate was plotted as a function of the concentration and the data for were fitted by least-squares nonlinear regression analysis using the equation $V=(V_{max}\cdot S)/(K_m+S)+K_d\cdot S$ (**FIG. 3**) in both jejunal and ileal cells, the predominant component of the uptake of CPT-11 lactone was non-saturable, suggesting uptake by either passive diffusion or fluid-phase endocytosis. The analysis of the curve of the uptake of CPT-11 carboxylate suggested also at least two separate components of the uptake process. The saturable component of the curve was characterized by a maximum rate of uptake (V_{max}) of 147 and 157 pmol$\cdot 10^6$ cell$^{-1}\cdot$min$^{-1}\cdot\mu$M^{-1} and a Michaelis constant (K_m) of 51.3 and 50.5 μM in jejunal and ileal cells, respectively. The minor non-saturable component was characterized by a diffusion constant (K_d)<0.05 pmol$\cdot 10^6$ cell$^{-1}\cdot$min$^{-1}\cdot\mu$M^{-1} and represented less than one twentieth of that for CPT-11 lactone in cells of both intestinal regions (Table 2). Furthermore, the Kd for CPT-11 lactone was 1.8-2.5 fold lower than that of SN-38 lactone.

[0068] The initial uptake rate of SN-38 lactone and carboxylate was plotted as a function of the concentration (**FIG. 4**). The maximum concentration of SN-38 used in this study was lower than 2 μM due to the poor solubility of the compound and therefore rendered the determination of the saturable and unsaturable component of the uptake difficult. In this range of concentrations, the uptake of SN-38 lactone and carboxylate was mostly non-saturable (**FIG. 4**).

[0069] The carrier-mediated transport is known to be inhibited by metabolic poisons, such as 2,4-dinitrophenol, which interferes with cell metabolism and reduces energy-producing reactions (23). Therefore, 2,4-dinitrophenol was used in applicants study to determine the mechanism of uptake of CPT-11 and SN-38 lactone and carboxylate, respectively. The results of this study are summarized in Table 3. Although, the uptake rate of both CPT-11 and SN-38 lactone was not significantly affected by the addition of 2,4-dinitrophenol, the uptake rate of CPT-11 and SN-38 carboxylate was reduced to 22.6 and 30.8%, respectively by 2,4-dinitrophenol, suggesting an active transport mechanism for both of these compounds.

[0070] 2,4-dinitrophenol-S-glutathione (DNP-SG) is known to be a substrate for the active multispecific organic anion transporter (cMOAT) in the liver (24). In addition, the conjugation by UDP-glucuronyltransferase of SN-38 leads to the formation of SN-38-Glu which is also a substrate for the hepatic CMOAT (12,17). To determine whether either CPT-11 carboxylate and/or SN-38 carboxylate is transported through a cMOAT-like mechanism in intestinal cells, the uptake rate of CPT-11 and SN-38 was studied in the presence or absence of both DNP-SG and SN-38-Glu. The results are summarized in Table 3. DNP-SG and SN-38-Glu significantly inhibited the the uptake of the carboxylate form of SN-38 by over 60% while that of CPT-11 carboxylate remained unchanged. The uptake rates of the lactone forms of CPT-11 and SN-38 were not significantly affected by the presence of either DNP-SG or SN38-Glu.

[0071] Micelle Formation and its Effect on the Initial Uptake Rate of CPT-11 and SN-38

[0072] Taurocholic acid (TCA) at a concentration greater than its critical micellar concentration forms micelles (25) which in contrast to both CPT-11 and SN-38, cannot pass through a 1,000-molecular weight cut-off membrane. We used this property to determine whether or not CPT-11 and SN-38 lactone and carboxylate can associate to the TCA micelles. The results reported in **FIG. 5**, show that TCA significantly decreased the % monomer concentration of CPT-11 lactone and carboxylate as well as SN-38 lactone. However, SN-38 carboxylate did not significantly associate to TCA micelles.

[0073] Next applicants tested the effect of micelle formation on the cellular uptake of CPT-11 and SN-38. In this series of experiments, the cells from the jejunum and ileum were combined. In the presence of 20 mM TCA, the initial uptake rate (mean±SD) of CPT-11 and SN-38 was reduced to 48.5±10.8 and 69.3±12.7% of control without TCA, respectively (n=5, Mann-Whitney test, p=0.015 and p=0.343 for CPT-11 and SN-38, respectively).

[0074] Effect of pH and Bicarbonate on the Initial Uptake Rate of CPT-11 and SN-38

[0075] The interconversion between the lactone and carboxylate CPT-11 and SN-38, respectively, is reversible and pH-driven (11). The effect of physiological pH (pH 6.2 to 8) on the initial uptake rate of 20 μM ^{14}C-CPT-11 and 2 μM ^{14}C-SN-38 was studied. The results summarized in **FIG. 6**, show that the uptake rate of CPT-11 and SN-38 significantly decreased by around 65% at a pH greater than 6.8. Alteration

of the uptake was also observed when the initial uptake rate of CPT-11 and SN-38 was measured in the presence and absence of bicarbonate. The uptake of CPT-11 and SN-38 was decreased when the HEPES component of the Hank's buffer was replaced by sodium bicarbonate and the pH adjusted to greater than 7.

[0076] Using hamster intestinal cells, the results of the present study show that the non-ionic, lactone forms of both CPT-11 and SN-38 were absorbed mainly through a passive mechanism but at a respective rate which was several times greater than their anionic carboxylate forms (Tables 1, 2 and 3; **FIGS. 2, 3** and **4**). There were significant differences in the transport mechanism as well as in the kinetic parameters between jejunal and ileal cells (Tables 2 and 3). Although not shown, similar results were also observed when the uptake of CPT-11 and SN-38 was performed using both cecal and colonic cells (26).

[0077] Isolated hamster intestinal cells are not the best model to estimate the cytotoxic effect of SN-38 due to their limited viability to around 2 hours (Gore et al., 1993). Therefore, HT29 cells were also used to study the comparative effects of physiological pH on both the initial uptake rate of 2 μM [^{14}C]SN-38 and the cytotoxicity of 0.4 μM SN-38. The initial rate of uptake of SN-38 was lower in HT-29 cells than in isolated hamster intestinal cells.(**FIGS. 3 and 4**). However, as observed in isolated hamster intestinal cells, the uptake rate of SN-38 in HT29 cells was significantly greater at pH 6.2 and 6.8, than at pH 7.4 and 8.0 (Kruskal-Wallis test:P=0.008, Dunn's method:$p<0.05$) (**FIG. 7**). The cytotoxicity of SN-38 for HT29 cells was significantly higher at pH 6.2 and 6.8 than at pH 7.4 and 8.0 (Kruskal-Wallis test:P=0.007; Dunn's method:$p<0.05$). **FIG. 5** shows the relationship between the initial rate of uptake of [^{14}C]SN-38 and the cytotoxicity of SN-38, indicating that, with decreasing pH, a higher uptake rate correlated with a more cytotoxic effect.

[0078] The results clearly showed that CPT-11 and SN-38 carboxylate were taken up by the intestinal cells through an active mechanism (Tables 2 and 3; **FIG. 3**). Recently, it has been proposed that cMOAT mostly expressed in hepatic canalicular membranes transports several types of organic anions into the bile as a primary active transport system (24, 27-29). Furthermore, the hepatic cMOAT has been reported to be responsible for the biliary excretion of the anions, SN-38 carboxylate, SN-38-Glu lactone and carboxylate (12, 17). The anion CPT-11 carboxylate was reported to be only partially eliminated through cMOAT (12, 17). The inventor's work shows that, in contrast to that of CPT-11 carboxylate, the initial uptake rate of SN-38 carboxylate was significantly inhibited by DNP-SG and SN-38-Glu (Table 3). These results are in accordance with those of Cho, et al (12, 17) using hepatic canalicular membrane vesicles. Therefore, this work underlines the involvement of a cMOAT or cMOAT-like transporter in jejunal and ileal cellular uptake of SN-38.

[0079] The inventors also reports that CPT-11 lactone and carboxylate, as well as SN-38 lactone can form micelles in the presence of high concentrations of TCA (**FIG. 5**). The percentage of the monomer concentration ranged from 38 to 47%. These concentrations differed from those of long-chain fatty acids (i.e. 2.3% for oleic acid) and from cholesterol (3%). Furthermore, micelle formation inhibited CPT-11 uptake, differing from the positive role bile acid micelle formation plays in the intestinal uptake of long-chain fatty acid and cholesterol. These results support data showing that micelle formation inhibited the uptake of short-chain fatty acids, such as palmitic acid.

[0080] As described in **FIG. 1**, the conversion from CPT-11 and SN-38 lactone to carboxylate is pH-driven (11, 12). It has previously been reported that at pH 7.4, 13% of SN-38 and CPT-11, respectively, were in their lactone form (30). The present study showed that the initial uptake rate of CPT-11 and Sn-38 was several times greater at acidic pH (pH 6.2 and 6.8) than that at neutral or alkaline pH (pH 7.4 and 8) (**FIG. 6**). Considering the fact that 1) at acidic pH, the non-ionic lactone form of CPT-11 and SN-38 are transported passively, 2) at neutral/basic pH, the anionic carboxylate form of CPT-11 and SN-38 are mostly absorbed actively, and 3) the uptake rates of both CPT-11 and Sn-38 lactone are several times greater than that of their carboxylate form, the mechanism of uptake of CPT-11and SN-38 by intestinal cells closely resembles that of short-chain fatty acids. This hypothesis will be supported by the fact that, as with short-chain fatty acids, micelle formation reduced the uptake of CPT-11 and SN-38 and that the uptake of CPT-11 and SN-38 is not limited to the small intestine but also takes place in the cecum and colon.

[0081] Therefore, as for short-chain fatty acids, alkalinization of bile and luminal content reduce the intestinal uptake of CPT-11 and SN-38. The biliary content of CPT-11 and its metabolites was determined for two men who were treated by cisplatin and received CPT-11 intravenously (9). The major component of the bile was CPT-11 (75.6-91.9%) while SN-38 and SN-38-Glu were minor components, 0.9-3.3% and 7.3-18.9%, respectively. Furthermore, the pH of human bile has been reported to range from 6.5 to 8.0 (31). It is therefore, considered that not only the carboxylate but also lactone the form of CPT-11 plays an important role in pharmacokinetics due to the greater absorption of CPT-11 lactone by intestinal epithelial cells, resulting in an increased level of CPT-11 in the enterohepatic circulation.

[0082] SN-38 is active mainly as the lactone form, while SN-38 carboxylate exhibits only minor topoisomerase I-inhibitory activity (32). Using rat whole body autoradiography, 24 h after IV injection of ^{14}C-SN-38, the radioactivity was found exclusively in the gastrointestinal tract (33). SN-38 exhibits strong cytotoxicity, SN38-Glu is a deactivated glucuronidated form of SN-38, and CPT-11 is much less cytotoxic compared to SN-38 (Kawato et al., 1991). Accumulation of SN-38 in the intestine was shown in rats (Atsumi et al., 1995), and was thought to be responsible for the diarrhea attributed to CPT-11 administration in nude mice (Araki et al., 1993). Disruption of the intestinal epithelium in the cecum was observed in mice and rats with diarrhea after CPT-11 administration (Takatsuna et al., 1996; Ikuno et al., 1995; Araki et al., 1993). The diarrhea induced by CPT-11 administration in human was reported to be secretory diarrhea (Bleiberg and Cvitkovic, 1996). However, as reported in the animal models, we observed lethal small-intestinal injury associated to CPT-11-induced side effects in patients (Kobayashi et al., 1998b).

[0083] Furthermore, accumulation of SN-38, the radioactivity was found exclusively in the gastrointestinal tract (33). Accumulation of SN-38 in the intestine was shown to be

responsible for the diarrhea attributed to CPT-11 in nude mice (34). Disruption of the intestinal epithelium in the cecum was thought to be responsible for CPT-11-induced diarrhea in rat (35). Finally, from clinical estimations in Europe, the diarrhea induced by CPT-1 was reported to be secretory diarrhea (36), while in our study applicants experienced severe incidence of small-intestinal injury (37).

[0084] Autopsy revealed the presence of pseudomembranes jejunoileitis, of which the appearance under light microscopy was characterized by the disruption of the intestinal epithelium, suggesting that damage diarrhea could occur in severe cases. A mechanism for CPT-11-induced diarrhea is believed to include the reabsorption of mainly lactone SN-38 and CPT-11, by the intestinal epithelium, resulting in a high exposure of the intestinal epithelium to these metabolites which causes structural and functional injuries to the intestinal tract.

[0085] As suggested in the present study, alkalization of bile and/or intestinal luminal content reduces the uptake of and the exposure of the intestinal epithelium to CPT-11 and SN-38 lactone. The absorption of short-chain fatty acids in the intestine has been studied for the past decade, and there have been reports of conflicting results. It is believed that decreasing pH induces an increased uptake of short-chain fatty acids, as reported in **FIG. 6**. Thus, a prevention treatment of camptothecin and CPT-11-induced diarrhea focuses on two objectives: 1) alkalinization of the intestinal lumen, and 2) clearance of CPT-11 and SN-38 from the body (i.e. stool control). A combination of sodium bicarbonate, magnesium oxide and water at pH greater than 7 is administered orally to patients prior and/or simultaneously with standard IV administration of CPT-11. The incidence of diarrhea is decreased.

[0086] The relationship between the cellular uptake of SN-38 and its associated cytotoxicity was also estimated in the present study. It was found that the cellular uptake and cytotoxicity of SN-38 in HT29 cells was pH-dependent, and that the cytotoxicity correlated well with the initial uptake rate (**FIG. 8**). As previously described, it is considered that at acidic pH, the predominant form of SN-38 is lactone. This would lead to both a greater cellular uptake and intracelluar concentration of SN-38 lactone. Since SN-38 is active mainly as the lactone form, while SN-38 carboxylate exhibits only minor topoisomerase I-inhibitory activity (Kawato et al., 1991), this should be associated to an increased cell death. Therefore, one possible mechanism for CPT-11-induced diarrhea might include the reabsorption of SN-38 lactone by the intestinal epithelium, resulting in structural and functional injuries to the intestinal tract.

[0087] In summary, the present study is the first to estimate the uptake of CPT-11 and SN-38 by intestinal epithelial cells. CPT-11 and SN-38 lactone are both passively transported, while both CPT-11 and SN-38 carboxylate are actively absorbed. The uptake rate of CPT-11 and SN-38 lactone is several times greater than that of the respective carboxylate form. Furthermore, the higher uptake rate of SN-38 is associated with an increased cytotoxic effect in HT29 cells. These findings suggest that the converstion to carboxylate would reduce the cellular uptake of both CPT-11 and SN-38. Consequently, these findings provide support for alkalization of the intestinal lumen as a possible mechanism to reduce reabsorption of CPT-11 and SN-38 in clinical practice. It is possible that limited intestinal reabsorption in turn modulates the bioavailability of this drug circulating enterohepatically, and reduces the toxic side effects of SN-38 on intestinal epithelium.

[0088] The results directly impact clinical practice, and administration of camptothecin compounds which are cleared through the liver, such as irinotecan hydrochloride and its derivatives. The inventors provide for oral alkalinization with the administration of camptothecin compounds which are cleared through the liver, including CPT-11.

[0089] In conclusion, the inventors describe the uptake of camptothecin compounds such as CPT-11 and SN-38 by intestinal epithelium. CPT-11 and SN-38 lactone are both passively transported by intestinal cells. Both CPT-11 and SN-38 carboxylate are actively absorbed, although through different transport mechanisms. The formation of micelles with TCA reduced the uptake of both CPT-11 and SN-38. The uptake rate of CPT-11 and SN-38 lactone is several times greater than that of the carboxylate form while the uptake rate decreased in the presence of bicarbonate and under condition of increased pH. These findings for CPT-11 and SN-38 can be useful in clinical practice.

[0090] Table I: Initial rates of uptake of CPT-11 and SN-38 by intestinal cells.

	jejunum		ileum	
CPT-11				
Lactone	85.6 ± 8.6	P < 0.001	80.9 ± 10.6	P = 0.001
Carboxylate	31.1 ± 3.8		31.1 ± 4.2	
SN-38				
Lactone	6.76 ± 1.08	P = 0.004	6.14 ± 1.02	P < 0.001
Carboxylate	1.70 ± 0.27		1.51 ± 0.20	

[0091] The initial rates of uptake of [^{14}C]CPT-11 (20 μM) and [^{14}C]SN-38 (2 μM), lactone and carboxylate, respectively, were compared. The results are expressed as p mol 10^6 cells^{-1} min^{-1} and are the mean ±SE of 10 experiments. Mann Whitney test was used for statistical analyses.

[0092] Table II: Kinetic Parameters of CPT-11 and SN-38 Uptake by Intestinal Cells

TABLE II

Kinetic parameters of CPT-11 and SN-38 uptake by intestinal cells

	jejunum			ileum		
	Km	Vmax	Kd	Km	Vmax	Kd
CPT-11						
Lactone	ND	ND	0.95 (0.15)	ND	ND	1.06 (0.28)
Carboxylate	51.3 (16.3)	146.9 (41.3)	<0.05 (<0.02)	50.5 (13.0)	157.3 (38.0)	<0.05 (<0.02)
SN-38						
Lactone*	ND	ND	2.38 (0.26)	ND	ND	1.87 (0.10)
Carboxylate*	ND	ND	0.44 (0.17)	ND	ND	0.42 (0.01)

[0093] (*): Because of limited solubility, only concentrations of SN-38 up to 2 μM were investigated.

[0094] (*): Because SN-38 carboxylate is judged to be actively transported from the estimation of its uptake in the presence of dinitrophenol (Table 3), these values are not considered to be physiologically relevant.

[0095] NOTE: The data were fitted by least-square non-linear regression analysis using the equation $V=(V_{max}\ S)/(K_m+S)+K_d\ S$. V_{max} (p mol 10^6 cells^{-1} min^{-1}) is the maximum rate of uptake, K_m (μM) is the apparent Michaelis constant, K_d (p mole 10^6 cells^{-1}●min^{-1} μM^{-1}) is the rate of diffusion and S (μM) is the concentration of either CPT-11 or SN-38. Values are mean ±SE. The major component of the uptake of CPT-11 lactone, SN-38 lactone and SN-38 carboxylate, respectively, was non-saturable and therefore, the K_m and V_{max} values were not determined (ND).

[0096] Table III: Effect of Dinitrophenol, SN38-Glu and DNP-SG on Initial Uptake Rate of CPT-11 and SN-38

TABLE III

Effect of dinitrophenol, SN38-Glu and DNP-SG on initial uptake rate of CPT-11 and SN-38

	CPT-11 carboxylate		SN-38 carboxylate		CPT-11 lactone		SN-38 lactone	
	jejunum	ileum	jejunum	ileum	jejunum	ileum	jejunum	ileum
Dinitrophenol (1 mM)								
Mean	22.6	29.2	25.5	30.8	94.1	105.5	96.1	134.9
(SE)	(13.5)	(9.2)	(12.4)	(13.1)	(18.4)	(15.6)	(14.7)	(19.0)
P value[1](n = 5)	0.016	0.008	0.008	0.016	NS	NS	NS	NS
SN38-Glu (200 μM)								
Mean	108.9	93.9	40.1*	28.9*	88.9	NE	54.3	NE
(SE)	(22.1)	(14.3)	(11.1)	(11.2)	(15.3)		(20.6)	
DNP-SG (200 μM)								
Mean	103.2	105.8	32.0*	28.5*	105.4	NE	78.8	NE
(SE)	(17.0)	(36.3)	(9.9)	(11.9)	(12.7)		(24.4)	
p value[2] (n = 5)	NS	NS	0.007	0.020	NS		NS	

NE, not estimated; NS, not significantly different from control

NOTE: Dinitrophenol, SN-38 glucuronide (SN38-Glu) or 2,4-dinitrophenyl-S-glutathione (DNP-SG) was added to the indicated cell suspension before the addition of [^{14}C]CPT-11 (20 μM) and [^{14}C]Sn-38 (2 μM), respectively (for details, see Materials and Methods). The initial uptake rate of CPT-11 and SN-38 in the presence of each compound was expressed as percentage (%) of control. Differences between dinitrophenol and its control were evaluated by [1]Mann-Whitney test. Differences among SN-38Glu, DNP-SG and their control were evaluated by [2]Kruskal-Wallis test, and the significant difference from respective control was analyzed according to Dunn's method (*$p < 0.05$).

[0097] Irinotecan Hydrochloride Formulations

[0098] In a preferred embodiment sodium bicarbonate, magnesium oxide and water are administered at more than a pH of about 7, preferably pH of 8 to 10 and most preferably

a pH of 8 to 9, provided to patients treated with camptothecin compounds such as CPT-11 and its derivatives.

[0099] Further, the CPT-11 compounds of the present invention are useful in pharmaceutical compositions for systemic administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, suppositories, sterile parenteral solutions or suspensions, sterile non-parenteral solutions or suspensions oral solutions or suspensions, oil in water or water in oil emulsions and the like, containing suitable quantities of an active ingredient. For oral administration either solid or fluid unit dosage forms can be prepared with the compounds. The compounds are useful in pharmaceutical compositions (wt %) of the active ingredient with a carrier or vehicle in the composition in about 1 to 20% and preferably about 5 to 15%.

[0100] Either fluid or solid unit dosage forms can be readily prepared for oral administration. For example, the CPT-11 can be mixed with conventional ingredients such as dicalciumphosphate, magnesium aluminum silicate, magnesium stearate, calcium sulfate, starch, talc, lactose, acacia, methyl cellulose and functionally similar materials as pharmaceutical excipients or carriers. A sustained release formulation may optionally be used. Capsules may be formulated by mixing the compound with a pharmaceutical diluent which is inert and inserting this mixture into a hard gelatin capsule having the appropriate size. If soft capsules are desired a slurry of the compound with an acceptable vegetable, light petroleum, or other inert oil can be encapsulated by machine into a gelatin capsule.

[0101] Suspensions, syrups and elixirs may be used for oral administration of fluid unit dosage forms. A fluid preparation including oil may be used for oil soluble forms. A vegetable oil such as corn oil, peanut oil or safflower oil, for example, together with flavoring agents, sweeteners and any preservatives produces an acceptable fluid preparation. A surfactant may be added to water to form a syrup for fluid unit dosages. Hydro-alcoholic pharmaceutical preparations may be used having an acceptable sweetener such as sugar, saccharine or a biological sweetener and a flavoring agent in the form of an elixir.

[0102] Pharmaceutical compositions for parenteral and suppository administration can also be obtained using techniques standard in the art.

[0103] Suitable pharmaceutical carriers include-sterile water; saline, dextrose; dextrose in water or saline; condensation products of castor oil and ethylene oxide combining about 30 to about 35 moles of ethylene oxide per mole of castor oil; liquid acid; lower alkanols; oils such as corn oil; peanut oil, sesame oil and the like, with emulsifiers such as mono- or di-glyceride of a fatty acid, or a phosphatide, e.g., lecithin, and the like; glycols; polyalkylene glycols; aqueous media in the presence of a suspending agent, for example, sodium carboxymethylcellulose; sodium alginate; poly(vinylpyrolidone); and the like, alone, or with suitable dispensing agents such as lecithin; polyoxyethylene stearate; and the like. The carrier may also contain adjuvants such as preserving stabilizing, wetting, emulsifying agents and the like together with the penetration enhancer of this invention.

[0104] The effective dosage for mammals may vary due to such factors as age, weight activity level or condition of the subject being treated. Typically, an effective dosage of a compound according to the present invention is about 10 mg/m^2 to 700 mg/m^2 when administered by either oral or rectal dose from 1 to 3 times daily. CPT-11 may preferably be administered once a week for a 1 to 5 week period. Administration times and dosages of CPT-11 for the treatment of cancers and tumors are known.

[0105] Administration of Irinotecan Hydrochloride

[0106] The mean terminal elimination half-life of irinotecan hydrochloride (Pharmacia-Upjohn) is about 6 hours.

[0107] Camptothecin compounds may also be administered alone or in combination with combination chemotherapy regimens including leucovorin, cisplatin, 5-FU, oxiplatin as well as other known chemotherapeutics. In an alternative embodiment camptothecin compounds such as irinotecan hydrochloride may also be administered with loperamide. camptothecin compounds such as irinotecan hydrochloride may also be administered with loperamide.

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[0171] The purpose of the above description and examples is to illustrate some embodiments of the present invention without implying any limitation. It will be apparent to those of skill in the art that various modifications and variations may be made to the composition and method of the present invention without departing from the spirit or scope of the invention. All patents and publications cited herein are incorporated by reference in their entireties.

1. A method of inhibiting a diarrhea side effect of camptothecin compounds comprising administering said camptothecin compounds at an alkaline pH.

2. The method of claim 1, wherein the camptothecin compounds are selected from the group consisting of irinotecan hydrochloride (CPT-11), SN-38-Glu, SN-38 and its derivatives.

3. The method of claim 1, wherein the intestinal lumen and the bile is maintained at an alkaline pH.

4. The method of claim 1, wherein the irinotecan hydrochloride is administered intravenously, orally or intramuscularly.

5. The method of claim 1, wherein reabsorption of said camptothecin compounds by the intestines is inhibited.

6. A method of treating cancer comprising administering irinotecan hydrochloride and its derivatives while maintaining the intestinal lumen at an alkaline pH.

7. The method of claim 6, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, colon cancer, malignant melanoma, small cell lung cancer, thyroid cancers, lymphomas and leukemias.

8. The method of claim 6, wherein the alkaline pH is a pH from 7 to 10.

9. The method of claim 6, wherein the alkaline pH is a pH from 7.

10. The method of claim 6, wherein the alkaline pH is a pH from 8.

10. The method of claim 5, wherein the alkaline pH is a pH from 9.

11. The method of claim 5, wherein the alkaline pH is a pH from 10.

12. A method of treating AIDS comprising administering irinotecan hydrochloride or its derivatives while maintaining the intestinal lumen at an alkaline pH.

13. A method of treating cancer comprising administering a compound selected from the group consisting of 7-hydroxy-methyl camptothecin, irinotecan hydrochloride, aminocamptothecin, DX-8951F, SN-38, HAR4, HAR5, HAR6, HAR7, HAR8 and topotecan, while maintaining the intestinal lumen at an alkaline pH.

14. A kit comprising a pharmaceutical composition including irinotecan hydrochloride (CPT-11) in combination with a suitable amount of bicarbonate to maintain the intestinal lumen at an alkaline pH.

15. The composition of claim 14, wherein the bicarbonate is selected from the group consisting of sodium bicarbonate, magnesium bicarbonate, potassium bicarbonate and mixtures thereof.

16. A method of administering a camptothecin compound comprising prior to or simultaneously administering said camptothecin compound, orally administering a composition comprising borbic acid.

17. A method of administering a camptothecin compound comprising prior to or simultaneously administering said camptothecin compound, orally administering a composition comprising urso-deoxycholic acid.

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